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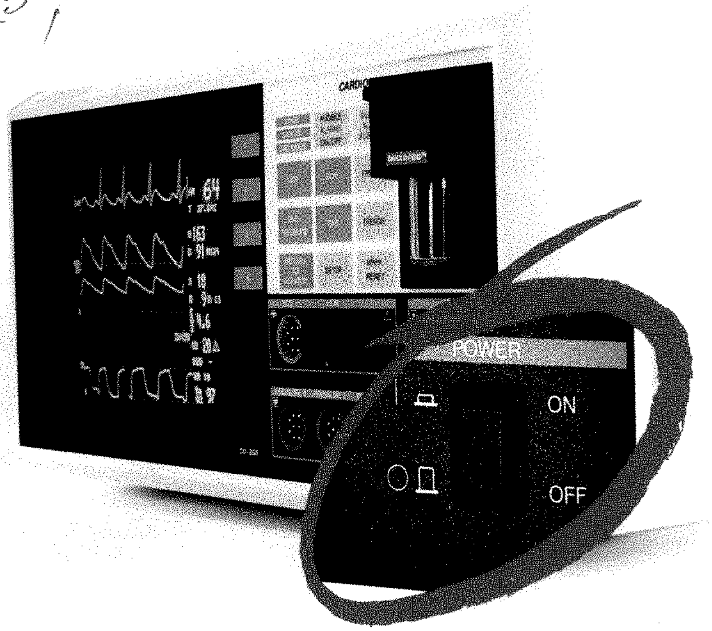

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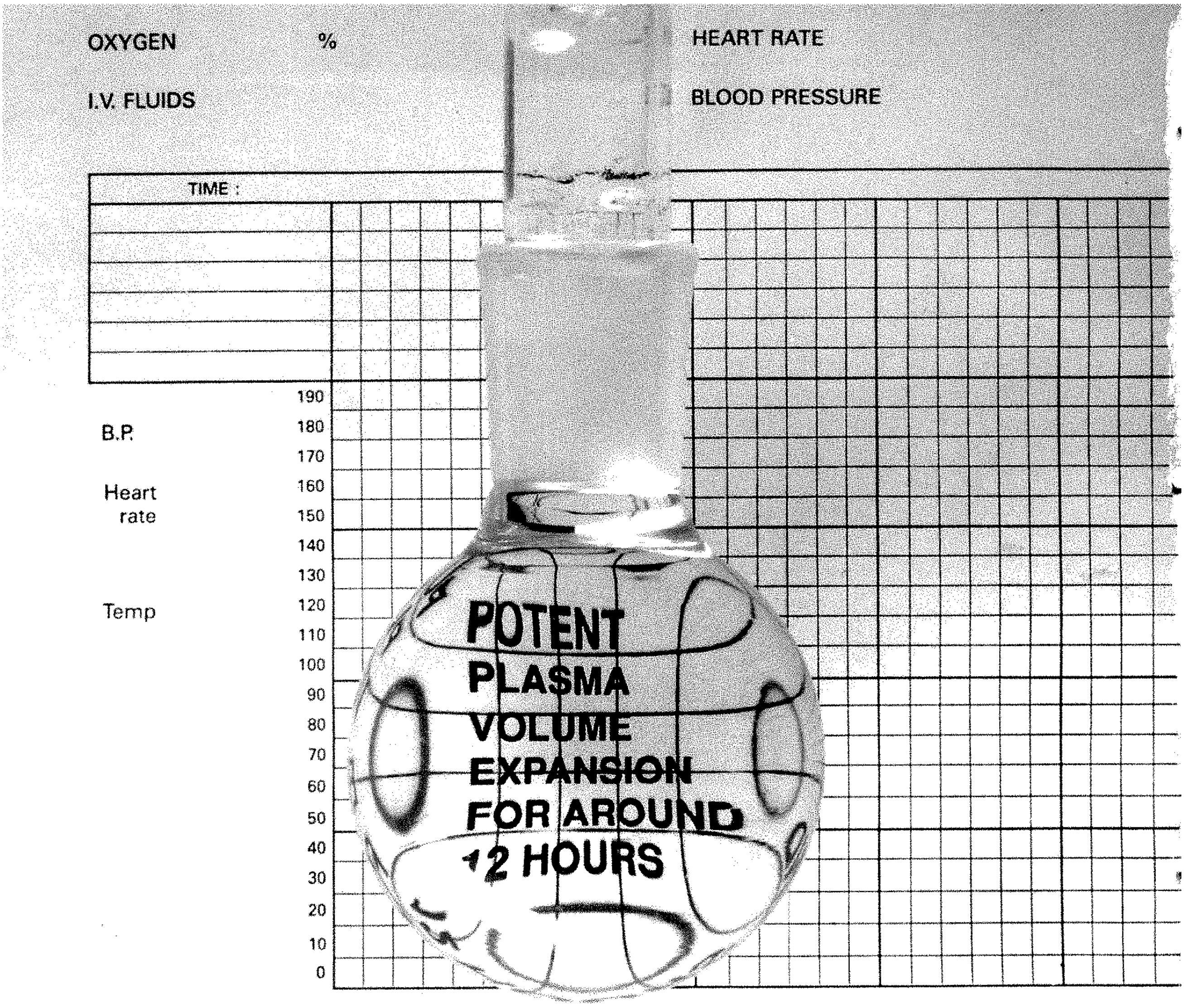

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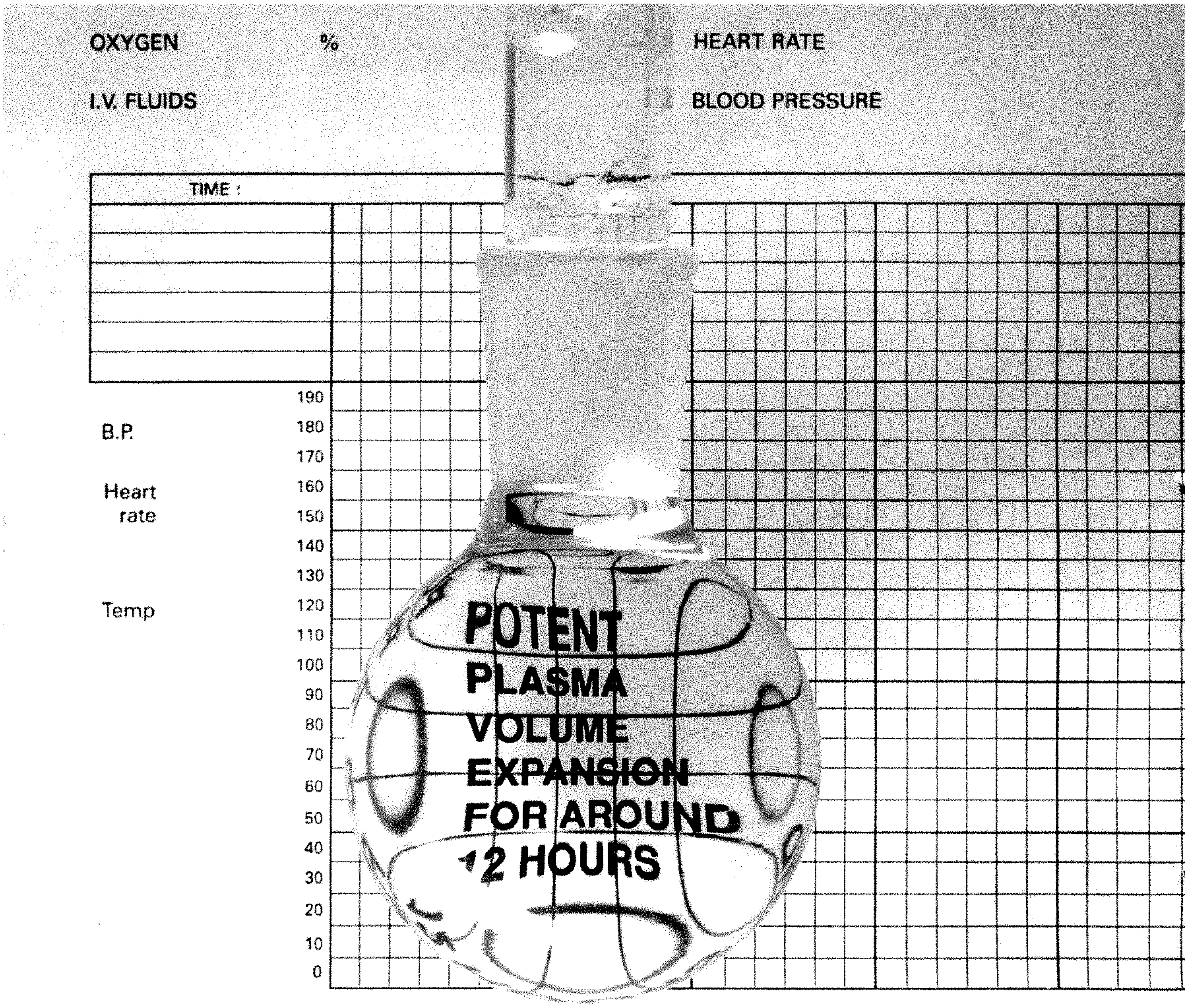

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

ASPIRIN AND EXTRADURAL BLOCKS

Although the medicinal effects of salycin derived from the willow bark had been known for several centuries, it was 1860 [1], before acetysalicylic acid was manufactured. Dresser introduced aspirin into medical practice in 1899, and by the beginning of this century its main therapeutic actions were generally accepted: antipyretic, anti-inflammatory and analgesic. These remained the main indications for the use of aspirin until the late 1970s, when its effectiveness as an antiplatelet agent became increasingly apparent. Since then, aspirin therapy has been used widely as an antithrombotic agent [2], prompting the phrase "new uses for an old drug" [3].

This has presented the anaesthetist (especially the obstetric anaesthetist) with a dilemma. There is no controversy regarding the performance of an extradural block in patients who are fully anticoagulated or have a coagulopathy; these are absolute contraindications. However, aspirin therapy, by its antiplatelet activity, may increase the risk of formation of extradural haematoma with potential disastrous sequelae, thus making extradural anaesthesia inadvisable, even though regional anaesthesia may be the technique of choice in many patients, both obstetric and non-obstetric, for whom aspirin therapy has been prescribed.

It is important to consider the role of aspirin in haemostasis and the risks of vessel puncture associated with performance of an extradural block.

A similar sequence of biochemical reactions in platelets and in the endothelial cells of blood vessels synthesizes two radically different end products with opposing biochemical/physiological properties [4, 5]. Thromboxane A_2 (TxA_2) from platelet phospholipid constricts large blood vessels, variably constricts smaller vessels and is a potent stimulus for platelet aggregation. Prostacyclin, the end product of phospholipid metabolism in the endothelial cells, causes vasodilatation and is the most potent known *inhibitor* of platelet aggregation. There is some biochemical co-operation as, in the presence of trauma, vascular endothelium may synthesize prostacyclin from platelet endoperoxidases in addition to its own endoperoxidases. It is the *balance* between TxA_2 and prostacyclin which is important in vascular haemostasis. Tilting the balance in favour of prostacyclin results in vasodilatation and decreased platelet aggregation. Pharmacologically, this may be achieved either by administration of prostacyclin or by *inhibition* of TxA_2 production.

Aspirin inhibits the enzyme cyclo-oxygenase which is responsible for the formation of the prostaglandin endoperoxidases, common precursors of TxA_2 and prostacyclin. Formation of both end products is inhibited. The effect of aspirin on vascular endothelial cyclo-oxygenase is of shorter duration [6] and requires doses of 1–1.5 g 24 h^{-1}. *Low dose* aspirin (30–40 mg daily), however, theoretically inhibits platelet cyclo-oxygenase, thus reducing TxA_2 production and tilting the balance in favour of prostacyclin, leading to vasodilatation and inhibition of platelet aggregation. The effect of aspirin on platelets is irreversible and persists for the life of the platelet (7–10 days). Bleeding may be prolonged, therefore, for several days after the drug is discontinued.

Arrest of bleeding from damaged vessels depends on the three components of haemostasis: the reaction of the vessels themselves at the site of injury (vasoconstriction); formation of an adequate platelet plug at the site of injury; activation of the clotting cascade.

By reducing the synthesis of TxA_2, low dose aspirin inhibits the first two components of haemostasis—therefore the bleeding time may be prolonged. Kyrle and colleagues [7], in an elegant study, demonstrated a reduction in TxA_2 concentrations and TxA_2 generation in blood from bleeding time tests. There was also a reduction in δ-granule release from the platelets and some inhibition of thrombin formation, suggesting that the third component of haemostasis is also affected.

Although serious neurological sequelae [8, 9] following extradural analgesia are rare and the incidence of paraplegia is less than 1:10000, one of the most important factors contributing to paraplegia is extradural bleeding with formation of haematoma [10]. When an extradural vein is punctured, by either the needle or the catheter, in an aspirin-treated patient, the scenario is set for the risk of development of an extradural haematoma. Factors increasing extradural venous pressure [11] (for example coughing, straining, pregnancy, maternal expulsive efforts during second stage, patient restlessness, etc.) are likely to increase bleeding or displace the fragile platelet plug, or both.

What are the risks of vessel puncture associated with extradural analgesia? In studies [12] relating to obstetric patients, the incidence may be as high as 18%. Clinically, vessel puncture is rare in the non-obstetric population, but as the sequelae of an extradural haematoma are potentially disastrous, some assessment of platelet function *must* be made in aspirin-treated patients. Measurement of the bleeding time is the only practical test of *in vivo* platelet function. Described originally by Duke [13] in 1910, this test has undergone many modifications. Meticulous attention to detail and a standard technique is required to achieve reproducible results. The modified Ivy technique using a surgicutt [14] (similar to a Simplate) device is mastered easily by motivated clinicians and does not require the attendance of a specialized haematology technician. Mielke [15] has reviewed the practical aspects (venostasis, direction of the incision, cuff pressure, etc.) of measurement of the post-aspirin bleeding time. A bleeding time kit, with instructions, should be available in all clinical areas where extradural blocks may be performed.

The upper limit of a normal bleeding time is 10 min and it has been suggested that this should be the upper limit for minor surgery [16]; insertion of an extradural catheter is similar. Although the bleeding time may return to normal in 72 h after aspirin therapy has been discontinued, it may take 7–10 days for *in vitro* platelet aggregation tests to return to normal [17]. As new biochemically normal platelets are formed, the plug becomes less fragile and may be adequate for *small* vascular lesions.

It may be suggested that many extradural blocks are performed unknowingly in aspirin-treated patients, especially orthopaedic patients who frequently take aspirin-containing compounds for analgesia, and obstetric patients who self-medicate for minor ailments such as headaches. However, although vessel puncture is not so common in orthopaedic patients, there have been case reports of paraplegia following extradural anaesthesia [18] in this group, and since the thalidomide scare of the 1960s, the dangers of drug therapy in pregnancy have become obvious to the obstetric population. The increased use of extradural analgesia in obstetrics, certainly in the United Kingdom, did not occur until a decade later. An investigation in our maternity unit showed that very few obstetric patients now self-medicate.

Spontaneous extradural haematomata do occur without the combination of extradural blocks and antiplatelet or anticoagulant therapy [19], but if aspirin has been ingested it is not possible to state with certainty that the haematoma would have occurred irrespective of therapy.

The obstetric population provides the greatest dilemma for the anaesthetist. It has been shown that there is TxA_2/prostacyclin imbalance in pre-eclampsia, the placenta producing up to seven times more TxA_2 [20]. Obstetricians have sought to redress this imbalance both to prevent and to treat pre-eclampsia by administration of low dose aspirin [21, 22], and so far results have been encouraging. Extradural analgesia is frequently indicated specifically for labour and delivery in this group of obstetric patients. If the disease process is severe enough to reduce the platelet count to less than 100000 and prolong standard clotting tests, it is obvious that extradural analgesia is definitely contraindicated. What advice should be offered regarding the aspirin-treated patient? Preferably, aspirin therapy must be discontinued 7–10 days before delivery and a bleeding time test performed. Benzon, Brunner and Vaisrub [23] suggested that it was difficult to specify a bleeding time beyond which siting an extradural catheter could be considered unsafe. Perusal of the literature suggests that 10 min should be the cut off point, especially when other methods of analgesia and anaesthesia are available. The Devil's Advocate may enquire "what of the obstetric patient receiving aspirin therapy and in whom tracheal intubation is expected to be difficult or impossible?"

The problem with extradural anaesthesia is that bleeding may occur no matter how skilfully the technique is performed. However, anaesthetic techniques and the quality of equipment available are improving. Either spinal anaesthesia with a narrow gauge needle or a continuous subarachnoid block using a microcatheter might be more appropriate. Postoperative neurological monitoring should be undertaken in all aspirin-treated patients who have received regional anaesthesia. Taking his or her own skill and experience into consideration, the anaesthetist should balance all risks present in any individual situation. Success and absence of complications with one patient should not become the *raison d'être* for treating all patients similarly.

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EDITORIAL II

DEEP VENOUS THROMBOSIS AND ANAESTHESIA

It is only in the past 10 years that clinical studies have suggested that anaesthesia may influence the incidence of deep venous thrombosis (DVT) and also, possibly, pulmonary thromboembolism (PTE). Much of the evidence is far from conclusive, but work on the possible mechanisms of the effects of anaesthetic techniques and drugs has shown some fascinating and often entirely unexpected phenomena.

The method of detection of DVT is crucial to the reliability of the results; the "gold standard" is ascending venography or phlebography [1]. This is highly accurate and reliable, but too invasive, expensive and time consuming for routine clinical use. The fibrinogen uptake test (FUT) uses radio-labelled fibrinogen which is injected before operation and a scan is used non-invasively to detect incorporation of fibrinogen into newly formed thrombus. Unfortunately, while this is accurate for clots below mid thigh, in hip surgery it is associated with a false positive rate of more than 30% [2]. This reduces its role to that of a screening technique. The risk of transmission of hepatitis B is a further disadvantage. In addition, it is of little use for detection of existing thrombi. Detection of DVT by clinical signs is so unreliable as to have no place in research [1].

Not surprisingly, workers in the field have chosen groups of patients at high risk of DVT and PTE, mainly those undergoing surgery for hip replacement and repair of hip fracture. All studies which have reported a difference in incidence of DVT with anaesthetic technique have compared extradural or subarachnoid block (SAB) with general anaesthesia (GA). In 1980, Thorburn, Loudon and Vallance [3] compared the incidence of DVT in patients after hip replacement. Fifty-three per cent of 47 patients in the GA group had DVT, compared with 29% of 38 patients who had SAB ($P < 0.05$). Patients were considered to have DVT only when clots were found by both FUT and venography. This study was not stated to have been randomized.

Modig [4, 5] has studied extensively patients having hip replacement, comparing the incidence of DVT and PTE (using perfusion lung scan) after GA with that after extradural block continued for 24 h. In both his major studies, Modig did not report the total DVT incidence, but he subdivided the incidence of thrombi into popliteal and femoral *vs* calf and thigh in the 1983 study [4], and thigh *vs* thigh and calf in the 1986 study [5]. In every case the incidence was significantly smaller in the extradural groups. Modig used venography 14 days before and 11 days after surgery. Coincidentally, in both studies, the incidence of PTE was shown by perfusion lung scan to be 33% after GA and 10% after extradural block. There were 60 patients in the 1983 study and 94 in the 1986 study. Presumably, even larger numbers would yield a conclusive result, but this author's verdict on these DVT results must be "highly suggestive but not proven".

Two studies have compared the incidence of DVT after repair of hip fracture under SAB or GA [6, 7]. Despite using completely different methods of detection, the results were almost identical. The study using FUT [6] found 76% of the GA group ($n = 37$) to have DVT, compared with 46% of the SAB group ($n = 37$). Venography was used in the other study [7] and showed DVT in 76% of the GA group ($n = 21$) and 40% in the SAB group ($n = 20$). Both of these results are statistically significant. It is an enigma that the FUT results should be almost identical to the venogram results, despite the above comments on FUT.

A study by Hendolin, Mattila and Poikolainen [8] comparing extradural block and GA for incidence of DVT in open prostatectomy should be discounted, as a significant reduction in DVT in the extradural group was shown by FUT but not by venography; this demonstrates that the FUT had a false positive rate of just over 30%.

The sparse number of positive studies is expanded significantly by the study reported in this issue by Jørgensen and colleagues [9], of patients undergoing knee replacement. DVT incidence (by venography) was significantly smaller in the extradural group; 18%, compared with 59% in the GA group. Two aspects of this excellent study are unique in the area of anaesthesia and DVT. First, the use of a tourniquet leading to total intraoperative stasis and thus denying the assumed intraoperative advantage of extradural block in decreasing stasis. Second, the prolongation of analgesia with low dose bupivacaine for 3 days in the majority of patients. All patients wore graded compression stockings.

Studies yielding negative results may be supremely valuable in many ways. Those comparing the incidence of DVT where thoracic as opposed to lumbar extradural analgesia was used have shown no effect on incidence of DVT [10, 11]. It is also interesting that a study by Fredin and Rosberg [12] found that when all patients received dextran there was no difference in DVT incidence after hip replacement under either extradural or GA. However, the incidence was approximately 45% overall, which is almost that which one would expect in a GA group with no prophylaxis.

Summarizing the clinical evidence, it would seem that SAB is associated with a reduction in DVT in hip replacement and hip fracture repair, but that the evidence for an effect of extradural block in these procedures, while consistently suggestive, is not yet conclusive. Extradural block in knee replacement is, however, associated with a reduced incidence of total DVT.

General anaesthesia has been known for many years to reduce lower limb blood flow by about 50% [13, 14]. However, although in theory positive pressure ventilation should worsen the situation by further impeding venous return, this has not been shown to increase either incidence of DVT [15] or overall mortality [16].

Lumbar (but not thoracic) extradural and subarachnoid block produce vasodilatation of the lower limbs. Modig [17] has shown increased arterial inflow and venous emptying rate associated with extradural block. It is likely that not only vasodilatation but also a reduction in blood viscosity are important in this situation. Patients with SAB or extradural block are commonly given a fluid load, reducing PCV and thus reducing viscosity. Vasodilatation, by decreasing intravascular hydrostatic pressure, further reduces viscosity. SAB has been shown [18] to reduce viscosity still further by increasing the deformability of red cells, white cells, or both. General anaesthesia, however, decreases red cell deformability *in vivo*, and halothane *in vitro* does so in a dose dependent manner. An explanation for these changes has not yet been determined.

Modig and colleagues [19] have also shown that extradural block is associated with significantly less inhibition of fibrinolysis than occurs after GA, associated with an increase in concentration of plasminogen activators. In addition, activation of factor VIII was significantly less after extradural compared with GA.

It may be that local anaesthetic agents themselves are important in mediating a prophylactic effect. Cooke and colleagues [20] infused lignocaine 2 mg min^{-1} for 6 days to patients having hip replacement. No patient developed DVT in this group by 7 days after surgery. By 14 days, only 14% had DVT, compared with 78% in the control group. This extraordinary study surely merits confirmation.

Local anaesthetic agents are known to inhibit platelet adhesion [21], aggregation and release [22], leucocyte migration and aggregation [23], and lignocaine causes a small reduction in blood viscosity [24]. At first sight, the study in this issue [9] appears to cast doubt on the value of intraoperative improvement in blood flow as an important mechanism of prevention of DVT, as all patients had tourniquets. However, tourniquets have been shown not to affect risk of DVT [25] and indeed promote release of plasminogen activators, albeit lasting only for a short time after deflation of the cuff. The prolonged extradural analgesia in this study and in that of Modig and colleagues [19] may be important in reducing DVT risk.

Methods of reducing DVT abound, but only one—full preoperative anticoagulation with phenindione [26] (a warfarin-like compound)—has been shown to reduce overall mortality. Where does regional analgesia stand in this respect? As far as its effect on mortality in hip replacement is concerned, we do not know. A very large study indeed would be needed, as mortality is around 1.6% [27]. In patients with fractured hips, a reduction in early postoperative mortality associated with SAB has been shown by several studies [28–30] and the time course is consistent with a reduction in thromboembolic events. However long-term outcome is unaffected [29–31].

Other questions also remain unanswered. Should we use SAB or extradural analgesia in patients receiving low-dose heparin or those receiving aspirin or other anti-platelet agents? If we do, what degree of haematological investigation is sufficient?

Perhaps the topic could be summed up by the depressingly appropriate quotation of Mitchell [32]: "What we have is not what we want; what we want is not what we need; what we need is not what we can obtain."

P. J. McKenzie

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ANTITHROMBOTIC EFFICACY OF CONTINUOUS EXTRADURAL ANALGESIA AFTER KNEE REPLACEMENT

L. N. JØRGENSEN, L. S. RÅSMUSSEN, P. T. NIELSEN, A. LEFFERS AND E. ALBRECHT-BESTE

SUMMARY

We have studied the effect of extradural analgesia on postoperative venous thrombosis in patients undergoing knee arthroplasty. Forty-eight patients were allocated randomly to receive either general anaesthesia or extradural analgesia with local anaesthetics for 3 days. All patients wore compressive elastic stockings and no anticoagulant drugs were administered. Bilateral venography was performed 10 days after surgery. Continuous extradural analgesia did not impede mobilization of the patients. One case of non-fatal pulmonary embolism occurred in a patient who received general anaesthesia. The use of continuous extradural analgesia resulted in a significant difference in the total incidence of deep vein thrombosis (18% compared with 59% after general anaesthesia (P = 0.02)). The incidence of calf vein thrombosis was 12% compared with 45% after general anaesthesia (P = 0.05).

KEY WORDS

Anaesthetic techniques: extradural. Complications: thrombophlebitis. Surgery: orthopaedic.

Studies on patients undergoing knee arthroplasty suggest that this group of patients has a high incidence of postoperative deep vein thrombosis (DVT) [1–3]. Several investigations have shown that the incidence of DVT (demonstrated by venography) following hip surgery is reduced when the operation is performed under lumbar extradural or subarachnoid analgesia [4–7].

In the present study we have examined the effect of continuous lumbar extradural analgesia (EA) on the incidence of DVT after knee arthroplasty.

PATIENTS AND METHODS

The study was approved by the regional Ethics Committee and patients undergoing elective knee arthroplasty (primary or revision) gave informed consent to take part in the study. We excluded patients receiving antithrombotic medication, premenopausal women and those with a history of venous thromboembolic disease or allergy to radio-opaque contrast media. The patients were allocated randomly to either extradural anaesthesia (EA) or general anaesthesia (GA).

We considered 58 consecutive patients for inclusion in the study; three suffered from medical diseases which were contraindications to GA, and seven refused to enter the study. Hence, 48 patients were studied initially: 24 EA and 24 GA. Nine patients did not complete the study: five because of insufficient venography (technical problems, refusal by patient); two in whom Dextran 500 ml i.v. was administered during the operation; one in whom EA was insufficient and to whom GA was administered; and one subarachnoid anaesthesia. Thus data were obtained on 39 patients (table I).

All patients were premedicated with diazepam 0.3 mg kg^{-1} orally.

Continuous extradural analgesia

Before anaesthesia, all patients received an i.v. infusion of saline 1000 ml. With the patient in the horizontal lateral position, we administered a test dose of 2% mepivacaine 3 ml with adrenaline

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TABLE I. *Characteristics of the 39 randomized patients completing the study. EA = Extradural analgesia; GA = general anaesthesia*

	EA ($n = 17$)	GA ($n = 22$)
Age (yr) (median (range))	70.5 (52–87)	64.0 (38–85)
Sex (M/F)	4/13	7/15
Body mass index ($\mathrm{kg\ m^{-2}}$) (median (range))	27 (19–32)	27 (21–46)
Cardiac decompensation or arrhythmia	4	1
Varicose veins	2	3

followed by 2% mepivacaine 8–15 ml through a lumbar extradural catheter with its tip located approximately at the level of the third lumbar vertebra. If necessary, small doses of diazepam, fentanyl or both were given during surgery.

After operation, 0.25% bupivacaine 5 ml $\mathrm{h^{-1}}$ was infused through the extradural catheter by infusion pump (Perfusor, Secura, B. Braun). This dose was adjusted to achieve pain relief corresponding to a sensory block from L1–2 to L5/S1. In order to avoid interfering with routine mobilization, muscle function of the quadriceps of the non-operated leg was assessed frequently, and preserved by adjustment of the dose. This regimen was maintained until the third day after operation in 15 patients. The extradural catheter was removed on the second day in two patients in whom the neural block was insufficient.

General anaesthesia

Thiopentone 3–5 mg $\mathrm{kg^{-1}}$ was used for induction of anaesthesia. Before tracheal intubation, fentanyl 5 μg $\mathrm{kg^{-1}}$ and pancuronium 0.1 mg $\mathrm{kg^{-1}}$ were administered. Following tracheal intubation, the lungs were ventilated with 66% nitrous oxide in oxygen and diazepam 0.2 mg $\mathrm{kg^{-1}}$ administered i.v. Fentanyl was given intermittently during surgery in doses of 100 μg i.v. when appropriate, and muscle relaxation was maintained by intermittent administration of pancuronium 1–2 mg i.v. Residual neuromuscular block was antagonized with glycopyrronium 0.4 mg and pyridostigmine 10 mg. For postoperative pain relief the GA patients received i.m. injections of ketobemidone 5.0–7.5 mg on demand, and, when tolerated, ketobemidone 5–10 mg and paracetamol 1 g orally on demand.

Peri- and postoperative procedures

A standardized technique was used for all operations, with the patient in the supine position. An inflatable femoral tourniquet was applied after elevation of the leg. Before removal of the tourniquet a compressive elastic bandage was placed around the lower leg.

Anticoagulant prophylactic drugs were not administered, but patients wore thigh-length compressive elastic stockings (Comprinet, Beiersdorf) on the contralateral leg from before operation and a below-knee stocking on the other leg from the morning on the first day after operation. The stockings were not removed until the patient was ambulant.

All patients followed the same physiotherapy regimen with quadriceps exercises and active knee mobilization on the first day, and walking with full weight bearing on the second day after operation.

The volume of blood loss in the suction drains was assessed daily. In addition, the patients were examined routinely for signs or symptoms of DVT, pulmonary embolism, or both; if necessary, venography, ventilation–perfusion lung scan, or both, were carried out.

Bilateral ascending venography including exposure of the common and external iliac veins was performed 9–11 days after surgery as described by Rabinov and Paulin [8]. Iohexol (Omnipaque) 240 mg $\mathrm{ml^{-1}}$ was used as contrast medium.

The venograms were scrutinized by the same two experienced radiologists, who were unaware of the anaesthetic used. Diagnosis of DVT required a constant luminal defect in the deep veins on at least two projections visible to both radiologists. Defects apparent only in the communicating veins were not considered. The end-points sought were either absence of DVT based on bilateral venography, or occurrence of DVT based on uni- or bilateral venography.

Statistics

The Mann–Whitney two-sample rank sum test was used for comparison of unpaired data between two groups. The difference between two rates was evaluated by Fischer's test. $P < 0.05$ was regarded as statistically significant.

RESULTS

The groups were similar with respect to age, sex, body mass ratio, cardiac disease, presence of varicose veins (table I) and perioperative characteristics (table II). The total blood loss in

TABLE II. *Peri- and postoperative characteristics of 39 patients completing the study (median (range))*

	EA (n = 17)	GA (n = 22)
Duration of tourniquet inflation (min)	80 (55–100)	83 (55–105)
Total volume in drains (ml)	650 (340–1845)	950 (195–3275)
Transfusion requirements (number of packages)	0 (0–2)	0 (0–5)

TABLE III. *Incidence and location of DVT, and incidence of pulmonary embolism. Location refers to most proximal extension of the thrombus*

	EA (n = 17)	GA (n = 22)	P
Calf vein	2	10	0.05
Popliteal veins	1	0	
Femoral veins	0	3	
DVT (total)	3	13	0.02
DVT on non-operated side	1	1	
Symptomatic DVT	0	2	
Pulmonary embolism	0	1	

the drains did not differ significantly between the groups ($P = 0.4$).

Extradural analgesia was continued for at least 2 days after operation in the majority of the EA patients and no serious complications were observed.

The distribution and location of DVT in the two groups of patients are illustrated in table III. All patients with involvement of the popliteal or femoral veins also had venographic filling defects in calf veins. The use of EA was associated with a 17% incidence of DVT (95% confidence limits 2–36%), which was significantly less than the 59% incidence (36–79%) found in the GA group ($P = 0.02$). Only thrombotic lesions exclusively involving the lower leg veins were significantly fewer ($P = 0.05$). Only two cases of symptomatic DVT occurred, both in the GA group, and the thrombi were confined to the calf. Two patients had DVT only in the non-operated leg. One case of non-fatal pulmonary embolism was verified 5 days after operation in a patient in the GA group, in whom thrombotic lesions involved only the lower leg veins.

DISCUSSION

Several studies have shown that, following knee arthroplasty, the incidence of DVT (assessed by venography) is 40–80%, if prophylaxis has not been administered [1–3]. Most patients in these studies underwent surgery under GA. Despite the high risk of development of postoperative DVT, few randomized trials have been carried out using objective outcome measures to investigate prophylactic regimens for these patients. The incidence of DVT was reduced significantly in patients treated with intermittent pneumatic compression devices [9, 10], high dose aspirin [10], low dose warfarin [11], or antithrombin III combined with low dose heparin [12]. No effect was detected following use of either continuous passive knee motion [1] or low dose aspirin [10].

The present study has demonstrated that the use of continuous EA with local anaesthetics significantly reduced the incidence of calf vein thrombosis in patients undergoing knee arthroplasty. It is generally considered that thrombi located in the popliteal or femoral veins possess a higher embolic potential; the results of this study suggested that prevention of larger vein involvement might also be important, although this was not statistically significant. Assuming a 5% level of significance and an 8% minimum detectable difference of the incidence of proximal DVT, the statistical risk of failure to detect a real difference between the groups (type II error) was greater than 90%, because of the small number of patients studied. The typical distribution of the thrombi, with a predominance of calf vein lesions, is similar to that of other venographic studies [2, 3]. Similarly, we report a comparable incidence of symptomatic pulmonary embolism of 2%. When pulmonary scans were performed routinely after surgery, Stulberg and colleagues reported a 7% incidence of pulmonary embolism [12]. In other studies using bilateral venography, there is evidence of an antithrombotic effect from the use of regional lumbar anaesthesia in patients undergoing elective [4, 5, 7] and acute hip surgery

[6]. However, Modig and colleagues did not find a significant reduction in the incidence of *total* DVT [4, 5], and the patients in the study by Thorburn, Louden and Vallance were not randomized [7]. Interestingly, the incidence of postoperative pulmonary embolism assessed by ventilation–perfusion scintigraphy was reduced significantly in patients undergoing hip surgery under regional anaesthesia compared with GA. Modig's group also found that the postoperative incidence of pulmonary embolism assessed by ventilation–perfusion scintigraphy was reduced significantly in patients undergoing hip surgery under regional anaesthesia compared with GA [4, 5].

There may be several mechanisms to account for the prophylactic effects of EA. Regional lumbar block involving the L1 and L2 spinal nerves increases blood flow in the lower limbs [13]; there is also evidence that platelet aggregation and blood viscosity are reduced [14]. There are data suggesting that inhibition of coagulation and enhancement of fibrinolysis is induced by EA [15, 16], but these findings were not reproduced in a study by Rem and colleagues, who suggested that postoperative enhancement of coagulation, and impairment of fibrinolysis are regulated by factors other than neurogenic and adrenal [17].

Because of the use of tourniquets, it is clear that the protective role of EA against DVT in knee arthroplasty is not mediated by enhanced intraoperative blood flow. It is not clear if the antithrombotic effect of EA is mediated during or after surgery, but we used a 3-day duration of sympathetic block of vessels of the lower legs as most thrombi develop during this period [18]. We have no data to determine if a shorter regimen of EA would prove as beneficial.

The use of a tourniquet was postulated to reduce the incidence of DVT, but that study was uncontrolled [19]. Ischaemia caused by a tourniquet enhances local fibrinolysis, probably by release of tissue plasminogen activator from the vessel wall [19]. However, increased thrombolytic activity is short lived, and decreases to preoperative values within 30 min after deflation of the tourniquet. In two trials using well-matched control groups there was no difference in the incidence of DVT after surgery on the lower extremity with and without the use of a tourniquet [20].

Blood loss following various surgical procedures (hip [4, 5], hysterectomy, lower limb vascular surgery or amputation, and prostatectomy [21]) is decreased after lumbar regional anaesthesia compared with GA. In the present study, there was no significant difference in drainage, even though EA was prolonged for several days into the postoperative period.

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HYPNOTIC AND ANAESTHETIC ACTION OF THIOPENTONE AND MIDAZOLAM ALONE AND IN COMBINATION

T. G. SHORT, D. C. GALLETLY AND J. L. PLUMMER

SUMMARY

This study examined the interaction between i.v. administered midazolam and thiopentone on the loss of response to verbal command ("hypnosis") and the loss of response to transcutaneous electrical stimulation of the ulnar nerve ("anaesthesia") in patients presenting for minor elective surgery. Dose–response curves for thiopentone and midazolam individually and in combination were determined using the two end-points in 300 unpremedicated patients. For hypnosis a highly significant ($P < 0.001$) supra-addictive (synergistic) interaction was found, the combination having 1.8 times the expected potency of the individual agents. Although midazolam failed to produce anaesthesia in the dose range used, the dose of thiopentone required to produce anaesthesia was reduced by 50% in the presence of midazolam. The mechanism of interaction and the potential role of benzodiazepine–barbiturate combinations are discussed and the observed synergistic anaesthesia interaction is used to explain the potentially dangerous combination of benzodiazepines with other potent CNS depressants such as barbiturates and alcohol.

KEY WORDS

Anaesthetics, intravenous: thiopentone Hypnotics, benzodiazepines midazolam Pharmacology· dose–response curves, drug interactions, synergism.

The benzodiazepines and the barbiturates are believed to exert the majority of their sedative effects via an interaction with the gamma-aminobutyric acid_A (GABA_A) receptor–chloride ionophore [1,2]. Both agents influence GABA_A complex activity, causing enhancement of chloride channel conductance and thereby potentiation of the endogenously present, inhibitory neurotransmitter, GABA.

As benzodiazepines and barbiturates are frequently given during anaesthesia, the nature of their interaction with each other is of some interest. In this present study we have examined the interaction between thiopentone and midazolam on two end-points that correspond to hypnosis and anaesthesia.

PATIENTS AND METHODS

The study was performed on adult patients presenting for minor elective surgery. All gave informed consent to the study, which was approved by the local Ethics Committee. Patient criteria for entry into the study were: age 20–60 yr, ASA grade I or II, no recent ingestion of psychotropic medication and weight between −20% and +50% of ideal. All patients were unpremedicated.

In the first part of the study, dose–response relationships were established for thiopentone and midazolam given individually. Two hundred patients were allocated randomly to 10 groups of 20, each receiving one of five doses of thiopentone (2.5, 3.0, 3.5, 4.0 or 4.5 mg kg^{-1}) or one of five doses of midazolam (0.1, 0.125, 0.15, 0.175 or 0.2 mg kg^{-1}). All drugs were injected over 10 s into a large antecubital vein.

Patients were assessed for hypnosis and an-

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aesthesia 1.5 min after the thiopentone and 4 min after the midazolam, these times being the approximate time to peak effect of the two drugs when given as an i.v. bolus.

Hypnosis was assessed as failure to open eyes on verbal command. Anaesthesia was assessed only in those who had achieved hypnosis by applying, for up to 5 s, a standard transcutaneous 50-Hz tetanic stimulus (80-mA, 0.25-ms pulses) over the ulnar nerve in the forearm using a standard neuromuscular block monitor and adhesive gel electrodes. If there was no response or stiffening to this stimulus, except for that caused directly by nerve stimulation, the patient was judged to be anaesthetized, whilst movement to the stimulus was judged as "not anaesthetized" and the stimulus immediately discontinued. A similar method of electrical stimulation has been shown previously to be equivalent to the stimulation of surgical incision for determination of MAC [3].

In the second part of the study we examined thiopentone and midazolam given in combination, at doses based on the results of the individual dose–response curves. Beginning with a combination of one half the ED_{50} for hypnosis for each drug, we chose two doses smaller than this and two doses greater, whilst maintaining an approximately constant dose ratio for the two drugs. The following doses of thiopentone and midazolam, respectively, were used: 0.7/0.04, 1.1/0.06, 1.5/0.08, 1.9/0.1, 2.3/0.12 mg kg^{-1}. Five groups of 20 patients were studied with these combinations, using the same criteria for selection of patients, the same end-points for hypnosis and anaesthesia and the same observer for all patients. The timing of the method was altered, however, in order that assessment would occur at the same time as in the construction of the individual dose–response curves. Thus midazolam was administered first, followed 2.5 min later by thiopentone and then a further 1.5 min was allowed before assessment of hypnosis and anaesthesia.

Statistical analysis was performed using analysis of variance to compare age, weight, height and sex distribution between groups. For graphical display and calculation of ED_{50} values for hypnosis and anaesthesia the log (dose)–response curves were linearized using probit transformation [4].

Interactions using the hypnotic end-point were examined by modelling the joint effects of the drugs under the hypotheses of additive effects and non-additive effects. Proportions of patients who had achieved hypnosis with each treatment were converted to logits and the following additive model fitted to the data:

$$Y = \beta_0 + \beta_1 \log(T + (P.M)) \qquad (1)$$

where Y = logit transformed response; T = dose of thiopentone (mg kg^{-1}); M = dose of midazolam received (mg kg^{-1}); P = the relative potency at the appropriate effect level; β_0 and β_1 = parameters to be estimated. By multiplying the dose of midazolam by the relative potency it is converted into the "equivalent" dose of thiopentone; thus the term $T+(P.M)$ may be thought of as "total thiopentone equivalents". Analogously, the expression $M+(T/P)$ may be considered as "total midazolam equivalents" denoted by M_e, and is given by:

$$\log(P) = \beta_2 + \beta_3 \log(M_e) \qquad (2)$$

where $M_e = M + (T/P)$

The following model describing non-additive behaviour was fitted also to the data:

$$Y = \beta_0 + \beta_1 \log(T + P.M + \beta_4(T.P.M)^{0.5}) \qquad (3)$$

where β_4 is analogous to Finney's coefficient of synergism.

Combinations of the drugs were considered to be non-additive if equation (3) fitted the data significantly better than equation (1) [4, 5]. This method is an extension of that described by Finney [4] to the case of non-parallel log (dose)–response curves. A detailed description of this method of analysis including the data from this study as a worked example is the subject of a separate paper [5].

Because it was found that midazolam alone did not cause anaesthesia in the dose range chosen, the nature of the thiopentone–midazolam interaction using this end-point was examined by testing for a horizontal shift in the thiopentone log (dose)–response curve in the presence of midazolam. For this, the proportions of patients anaesthetized at each dose were converted to logits, and logistic log (dose)–response curves were fitted by weighted least squares [6] using SPSS-X.

RESULTS

There were no significant differences in the age, weight, height or sex between each group of 20

TABLE I. *Proportion of patients achieving hypnosis and anaesthesia following each dose of thiopentone, midazolam or a combination of the two. *Extreme data excluded from subsequent analysis*

Thiopentone (mg kg^{-1})	Midazolam (mg kg^{-1})	Proportion hypnotic	Proportion anaesthetized
2.5	—	0.25	0.2
3.0	—	0.45	0.2
3.5	—	0.75	0.45
4.0	—	0.90	0.60
4.5	—	1.00*	0.85
—	0.100	0.20	0
—	0.125	0.35	0
—	0.150	0.40	0
—	0.175	0.50	0
—	0.200	0.70	0
0.7	0.04	0.15	0*
1.1	0.06	0.45	0.05
1.5	0.08	0.75	0.15
1.9	0.10	0.95	0.60
2.3	0.12	0.95	0.80

patients or between the three drug groups. The mean age of the subjects in part one was 32 yr, weight 67 kg and height 166 cm; 75% of the patients were female. In part two, the mean age was 33 yr, weight 66 kg, height 164 cm; 75% of the patients were female. The proportions of patients that achieved hypnosis and anaesthesia following each dose of thiopentone and midazolam are displayed in table I.

For thiopentone, the ED_{50} for hypnosis was 3.0 mg kg^{-1} and that for anaesthesia was 3.6 mg kg^{-1} (fig. 1). For midazolam, the ED_{50} for hypnosis was 0.16 mg kg^{-1} and the slope of the curve was significantly flatter than the corresponding slope for hypnosis using thiopentone ($\psi^2 = 8.14$, d.f. = 1, $P < 0.005$) (fig. 2). No patient became anaesthetized in the midazolam group with the doses used. We did not pursue the dose–response curve for anaesthesia using midazolam with greater doses because, in a preliminary pilot study using midazolam 1 mg kg^{-1}, it was observed that even this large dose was incapable of suppressing movement to the standard 5-s transcutaneous tetanic simulation in a series of 10 patients.

The dose–response curve for hypnosis using the combination of thiopentone and midazolam is compared with the dose–response curves for the two individual agents in figure 3. The doses of thiopentone and thiopentone–midazolam have been expressed as "total midazolam equivalents" (M_e); thus the curves for thiopentone and midazolam when used individually now lie along the same line.

Thiopentone and midazolam acted synergistically in combination ($P < 0.001$). When using the combination in equieffective doses, 75% of patients became unconscious using a total dose equivalent to that which was effective in only 50% of patients using each agent individually. The coefficient of synergism (β_4) was 0.37. This implies that a dose of midazolam 0.1 mg kg^{-1},

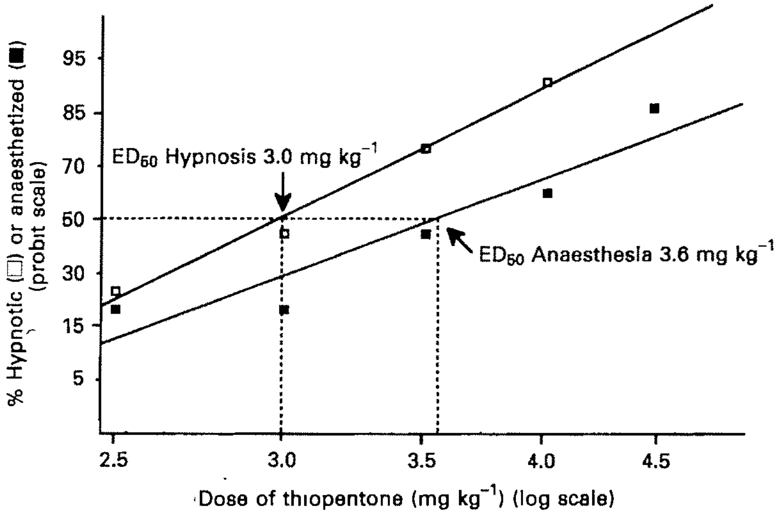

FIG. 1. Hypnotic and anaesthetic dose–response relationships for thiopentone. The ED_{50} for hypnosis was 3.0 mg kg^{-1} and that for anaesthesia 3.6 mg kg^{-1}.

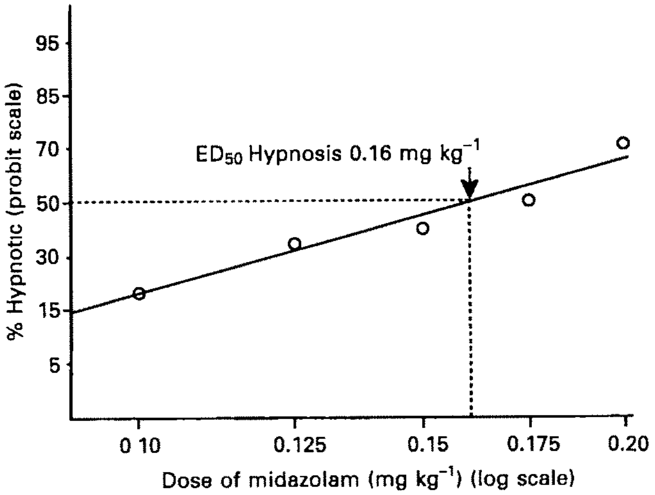

FIG. 2. Hypnotic dose-response relationship for midazolam. The ED_{50} for hypnosis was 0.16 mg kg^{-1}. No patient achieved anaesthesia with the dose range used.

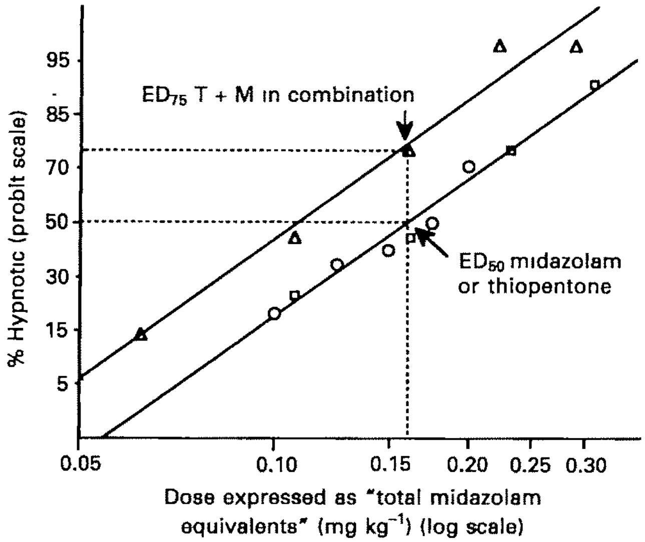

FIG. 3. Dose-response curve for hypnosis of combined midazolam and thiopentone (△), compared with the dose-response curves for the two individual agents (□ = thiopentone; ○ = midazolam). Doses of thiopentone and thiopentone-midazolam combinations have been converted to "total midazolam equivalents" (M_e)—see text. The curve for the combination is shifted significantly to the left, indicating synergistic interaction ($P < 0.001$). With the combination, 75 % of patients achieved hypnosis using a total dose equivalent to that which achieved hypnosis in 50 % of patients using each agent individually.

combined with a hypnotically equieffective dose of thiopentone (2.4 mg kg^{-1}), gave a response equivalent to midazolam 0.237 mg kg^{-1} ($0.1 + 0.1 + 0.037 = 0.237$) rather than to midazolam 0.2 mg kg^{-1} as would be expected if the drugs were additive.

The dose-response curves of thiopentone and the midazolam-thiopentone combination for anaesthesia are shown in figure 4. The addition of midazolam shifted the curve to the left ($P < 0.001$), with the slopes of the two curves not differing significantly ($P > 0.1$). The dose of

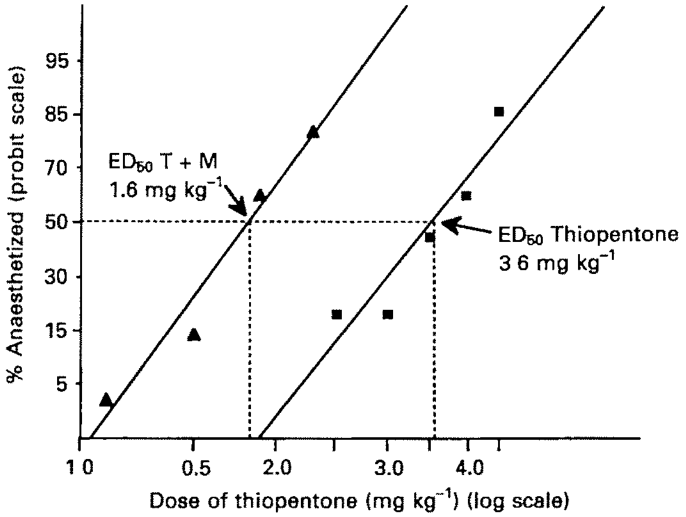

FIG. 4. Anaesthesia dose–response curves of thiopentone alone (■) and when combined with hypnotic doses of midazolam ($T+M$; ▲). The curve for the combination is shifted significantly to the left ($P < 0.001$) The addition of midazolam 0.1 mg kg^{-1} has reduced the dose of thiopentone required to achieve anaesthesia in 50% of patients from 3.6 to 1.8 mg kg^{-1}.

thiopentone required to anaesthetize 50% of the patients was reduced from 3.6 mg kg^{-1} to 1.8 mg kg^{-1} with the addition of midazolam 0.1 mg kg^{-1}.

DISCUSSION

Benzodiazepine agonists such as midazolam bind to the benzodiazepine receptor, at the GABA$_A$ receptor complex, to cause enhancement of affinity for the inhibitory neurotransmitter GABA and thereby potentiation of GABA-mediated chloride conductance, neuronal inhibition and, clinically, central nervous system depression [7, 8].

In contrast, the anaesthetic barbiturates exert their effects on chloride conductance through multiple effects at the GABA$_A$ receptor complex. Experimental findings suggest that: they enhance the binding of GABA to the GABA$_A$ receptor by making available a greater number of GABA receptors; they may slow the dissociation of GABA from its receptor; they enhance the affinity of the benzodiazepine receptor for the benzodiazepine; via interaction with the picrotoxin site, they enhance the coupling between GABA$_A$ receptor activation and chloride channel opening and, in high concentrations, they may directly open the chloride channel itself [2, 7, 8]. As GABA antagonists abolish the effects of barbiturates on chloride conductance, the direct channel effect may be of little importance [2]. The clear differences between benzodiazepine and barbiturate action are seen in chloride ion channel experiments in which benzodiazepines are observed to increase the frequency of channel opening, whereas barbiturates increase the duration of the open state [9]. It is possible that these various actions at the GABA$_A$ receptor complex account for most of the anaesthetic and sedative properties of the barbiturates.

In this present study, the ED$_{50}$ values for loss of response to verbal command of 3.0 mg kg^{-1} for thiopentone and 0.16 mg kg^{-1} for midazolam were comparable to values reported previously [10–12]. We observed that a significant supra-additive interaction occurred between midazolam and thiopentone, when combined, for both hypnotic and anaesthetic end-points. The finding for hypnosis is in agreement with previous observations of synergy in rats using loss of righting reflex as an end-point [13] and in patients using loss of response to verbal command [10].

Although we were unable to demonstrate any anaesthetic action by midazolam at the doses used, the drug caused a two-fold increase in the anaesthetic potency of thiopentone. With the addition of midazolam, the thiopentone ED$_{50}$ for anaesthesia was reduced from 3.6 mg kg^{-1} to 1.8

mg kg^{-1}. Thus, in the presence of thiopentone, the midazolam, which was added in doses hypnotically equieffective to the dose of thiopentone used, was acting as if it were an equieffective anaesthetic agent. This reduction in the anaesthetic dose of thiopentone is of similar magnitude to the reduction in MAC for volatile anaesthetic agents that occurs in the presence of a benzodiazepine: a 60% reduction in halothane MAC has been found in volunteers 30 min after diazepam 0.5 mg kg^{-1} i.m. [14] and a 34% reduction in halothane MAC has been observed following midazolam 0.2 mg kg^{-1} [15]. Perhaps of relevance to these findings is evidence that volatile anaesthetic agents such as halothane exert effects on the $GABA_A$ receptor similar to those of barbiturates in *in vitro* preparations [2, 16].

Previous authors have suggested that the synergistic interaction between thiopentone and midazolam on hypnosis is a result of barbiturate potentiation of benzodiazepine receptor binding [13]. The observed anaesthetic synergy, however, is difficult to explain simply on this basis because, even in very high doses (up to 1 mg kg^{-1}) associated with high receptor occupancy, we have observed no anaesthetic action of midazolam. As the benzodiazepine does enhance the anaesthetic effects of the barbiturate, our data are consistent with the $GABA_A$-ergic activity being important in the production of the anaesthetic state. Further, it has been observed that GABA receptor activation (by systemic administration of a GABA agonist, THIP) can induce a loss of righting reflex in rodents, although loss of response to a noxious stimulus is variable [17]. These observations might suggest, therefore, that neither exogenously administered GABA agonist nor benzodiazepine potentiation of endogenous concentrations of GABA is sufficient to cause anaesthesia with complete abolition of response to stimuli. It might be possible that further enhancement of GABA–chloride channel coupling or increase in GABA receptor numbers by addition of a barbiturate could increase channel conductivity to a level sufficient to produce loss of nociceptive response. We suggest, therefore, that the observed anaesthetic interaction between midazolam and thiopentone would be expected to occur if anaesthesia was associated with high chloride channel conductance and that the benzodiazepine modulation of $GABA_A$ receptor activity (itself incapable of achieving sufficient conductance) was potentiated by the barbiturate-induced changes in GABA–ionophore coupling, an increase in GABA receptor numbers, or both. In addition, it is possible that this combination of effects, together with enhanced benzodiazepine receptor affinity, might explain also the synergistic hypnotic action.

Several practical implications arise from the findings of this study. First, in clinical use, the presence of a benzodiazepine should potentiate the anaesthetic depth produced by thiopentone. Although we have not examined the cardiovascular or respiratory effects of the combination, it is possible that a benzodiazepine could be used to potentiate subanaesthetic concentrations of thiopentone for induction or maintenance of anaesthesia. A specific advantage of this synergistic combination is that the benzodiazepine component could be antagonized rapidly with the specific antagonist flumazenil, leaving the subanaesthetic background concentration of thiopentone. Conversely, because in some patients the dose of midazolam required to induce hypnosis is very large, the addition of a small dose of thiopentone could make benzodiazepine induction more reliable. As many other i.v. and inhalation anaesthetics may act in part through the GABA receptor, it is possible that an anaesthetic agent with a better recovery profile could be used instead of the barbiturate.

We were unable to demonstrate an anaesthetic effect for midazolam; however, the benzodiazepine markedly potentiated the anaesthetic effects of the barbiturate. This observation helps to explain why, although the clinically available benzodiazepines all have a high therapeutic index and when taken for intentional overdosage are relatively safe, their combination with low doses of barbiturate may result in deep levels of CNS depression which could be potentially fatal. Also, ethyl alcohol has an action similar to the barbiturates in that it potentiates the effects of GABA on chloride conductance, enhances benzodiazepine binding, increases the binding capacity of the low affinity GABA receptor and, at high concentrations, mimics the effect of GABA agonists at the GABA receptor. Unlike the barbiturates however, ethanol does not influence the kinetics of GABA binding and may be antagonized by certain benzodiazepine antagonists [18]. Because of the similarities, it would be expected that addition of a benzodiazepine to ethanol-induced intoxication would also have the potential to produce serious degrees of CNS depression. Thus the benzodiazepines can be considered safe only when used alone and not when combined with other drugs which may interact synergistically at the GABA complex.

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TEMAZEPAM ABSORPTION IN PATIENTS BEFORE SURGERY

H. E. HOSIE AND W. S. NIMMO

SUMMARY

We have compared the rates of absorption and efficacies of temazepam 30 mg in elixir and capsule formulations in 100 patients before surgery. Both formulations provided anxiolysis and sedation, but there was wide variation in plasma concentrations of temazepam between individuals and between formulations. The presence or absence of anxiety did not influence the absorption of the preparations. It is suggested that plasma concentrations in excess of 200 ng ml^{-1} are required for sedation and anxiolysis, and that this may be achieved more reliably using the elixir formulation.

KEY WORDS

Premedication: temazepam

Temazepam is used orally as a premedicant to provide anxiolysis and sedation. Its short duration of action allows rapid recovery without prolongation of sedation into the postoperative period [1].

Temazepam is available commercially in four forms in the United Kingdom and studies of its bioavailability and pharmacokinetics in different vehicles have been carried out in healthy volunteers [2–4]. In a previous study using an elixir formulation, wide variation in plasma concentration of temazepam was found at the time of surgery [5].

Preoperative anxiety may have an effect on gastric emptying and hence drug absorption [6, 7]. In a study of paracetamol absorption in patients awaiting operation, Simpson and Stakes showed that patients with low anxiety trait (AT) scores who had high anxiety state (AS) scores ($AS > AT$) before operation had delayed gastric emptying compared with patients who had anxiety state scores similar to or less than their trait scores ($AS \leqslant AT$) [6]. In other words, those with increased anxiety tended to have delayed gastric emptying.

The aims of this study were to compare the absorption and effects of temazepam in the capsule and elixir formulations in patients awaiting surgery, and to investigate the relationship between anxiety and absorption and the relationship between plasma concentration and effect.

PATIENTS AND METHODS

One hundred patients, aged 16–70 yr and ASA grades I or II, having elective surgery gave written informed consent to take part in the study, which was approved by the local Ethics Committee. Patients were excluded if they had a history of hepatic or renal disease, previous gastric surgery or gastrointestinal disease, were taking concomitant benzodiazepine therapy or drugs known to affect gastric emptying, or were pregnant.

Patients were allocated randomly to one of three groups: group 1 patients were given temazepam 30 mg in capsules with placebo elixir 15 ml; group 2 received temazepam 30 mg in elixir with placebo capsules; group 3 received placebo capsules and elixir. Nursing staff and patients were unaware of which medication had been used. The premedication was timed to be given 1 h before the start of surgery, but in most instances surgery did not commence until 2 h after premedication.

Venous blood samples were taken every 15 min for 2 h after premedication for assay of plasma

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concentration of temazepam by high pressure liquid chromatography (HPLC) [5].

Anxiety was assessed using the linear visual analogue anxiety scale (VAS) and the Spielberger State Trait Anxiety Inventory (STAI) [8]. The VAS comprised a 100-mm line with anxious/apprehensive and relaxed/confident end-points, and measurement from the "relaxed" end. The STAI is a reliable method of assessing anxiety which gives two scores: the anxiety state, which measures anxiety to the acute situation, and the anxiety trait, which represents an individual's anxiety about everyday situations ("chronic" anxiety).

Anxiety was assessed before premedication using the VAS and both parts of the STAI. Measurement of immediate anxiety was repeated 60 min after oral premedication using the VAS and the state anxiety component of the STAI.

Sedation was measured at 15-min intervals after premedication using a four-point self-rating scale. Patients classified themselves as awake, drowsy or sleepy and the observer classified them as asleep if they did not respond to verbal contact.

Statistical analysis of the data included analysis of variance and unpaired *t* tests for parametric data, Wilcoxon paired rank sum test and Mann–Whitney *U* test for non-parametric data, chi-square analysis for nominal data and the Spearmann rank correlation coefficient.

TABLE I. *Mean (range) age and weight, and sex distribution of patients*

	M	F	Age (yr)	Weight (kg)
Group 1				
Capsules	8	32	41	68.5
(*n* = 40)			(16–68)	(46.5–103)
Group 2				
Elixir	10	30	42	71.2
(*n* = 40)			(17–64)	(45.5–120)
Group 3				
Placebo	5	15	46	67.9
(*n* = 20)			(18–65)	47–96.5)

RESULTS

Forty patients were given temazepam in capsules (group 1), 40 received temazepam in elixir (group 2) and 20 placebo (group 3). There were no significant differences between the groups with respect to age, weight or sex (table I).

Plasma concentration of temazepam

Plasma concentration of temazepam were measured until induction of anaesthesia. Technical problems or early operation prevented analysis in three patients. In many patients temazepam was present in the first sample and this reflected residual drug following administration of a hypnotic dose on the previous evening.

There were no significant differences between the formulations, at any time, in mean plasma concentration of temazepam. Mean peak plasma concentrations of about 800 ng ml^{-1} occurred 30 min after premedication (table II).

There were marked differences in plasma concentrations both between individuals and between those given capsules and those premedicated with elixir (figs 1, 2). Peak plasma concentrations occurred at 15–105 min and varied

TABLE II. *Mean* (SEM) *plasma concentrations of temazepam (ng ml^{-1}) after oral temazepam 30 mg for the different formulations and in patients with low anxiety trait but high anxiety scores (AS > AT) and those with anxiety state scores similar to or less than their anxiety trait scores (AS ⩽ AT) before operation.* *P < 0.05 *compared with AS > AT at same time*

	Time (min)								
	0	15	30	45	60	75	90	105	120
Capsules	30	384	869	660	694	689	683	596	577
	(8)	(127)	(135)	(88)	(68)	(83)	(61)	(53)	(62)
Elixir	57	528	796	774	740	701	658	624	617
	(20)	(73)	(73)	(64)	(50)	(37)	(54)	(86)	(70)
AS > AT	38	410	938	789	777	674	608	549	575
	(9)	(87)	(106)	(69)	(60)	(51)	(43)	(54)	(63)
AS ⩽ AT	62	547	681	546*	614	753	764	682	619
	(27)	(171)	(139)	(95)	(67)	(77)	(74)	(85)	(126)

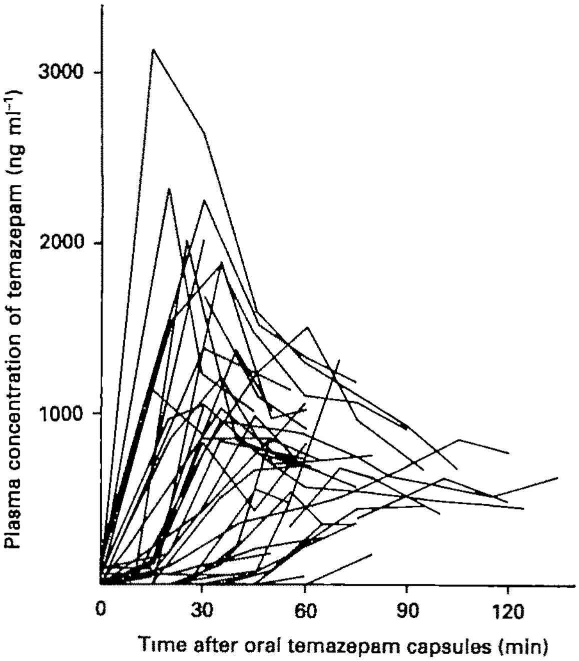

FIG. 1. Plasma concentrations of temazepam in patients given temazepam in capsule form.

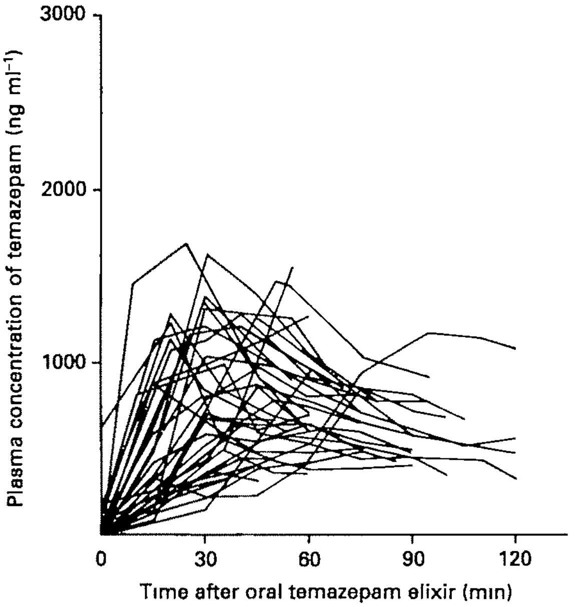

FIG. 2. Plasma concentrations of temazepam in patients given temazepam in elixir form.

from undetectable to 3100 ng ml^{-1}. The time to peak plasma concentration correlated inversely with age ($r = -0.475$; $P < 0.002$).

Anxiety

Patients were classified into two groups on the basis of their scores using the STAI. There was no difference in patient characteristics between the two groups. Overall, there was no significant difference in mean plasma concentrations between patients whose anxiety state score was greater than their anxiety trait score (AS > AT) and patients whose anxiety state was lower than or similar to their anxiety trait (AS $\leqslant$ AT), except at 45 min following premedication, when the concentration was significantly greater in the group AS > AT ($P < 0.05$) (table II).

Most patients were able to complete both the STAI and the visual linear analogue scale. Seven patients were unable to complete the assessments satisfactorily. One patient was transferred to theatre before the second anxiety assessment was made. The state score of the STAI and the visual analogue scale correlated well ($r = 0.668$; $P < 0.005$).

All three groups were found to have a similar degree of anxiety before premedication, using both methods of assessment. One hour after premedication, all three groups had reduced anxiety. This was significant in the groups given active temazepam, as judged with the visual linear analogue scale ($P < 0.01$), but was significant also in the group given placebo when assessment was made using the STAI score ($P < 0.05$) (figs 3, 4).

Sedation

For purposes of statistical analysis, patients were grouped as sedated (sleepy, drowsy and asleep) or unsedated (awake). Significant sedation was seen in the groups given active temazepam at 30, 45 and 60 min. There was no overall difference between capsules and elixir and no significant sedation was seen in the placebo group.

Correlation of plasma concentration with effect

Plasma concentrations of temazepam at 60 min correlated with change in anxiety and sedation using the Spearmann rank correlation. Rank correlation coefficients for anxiety were not statistically significant, but there was a significant correlation ($r = 0.339$; $P < 0.005$) between plasma temazepam concentration and sedation.

The mean plasma concentration of temazepam was calculated for each sedation rating (table III)—"awake" was associated with a mean plasma concentration of temazepam 211 ng ml^{-1},

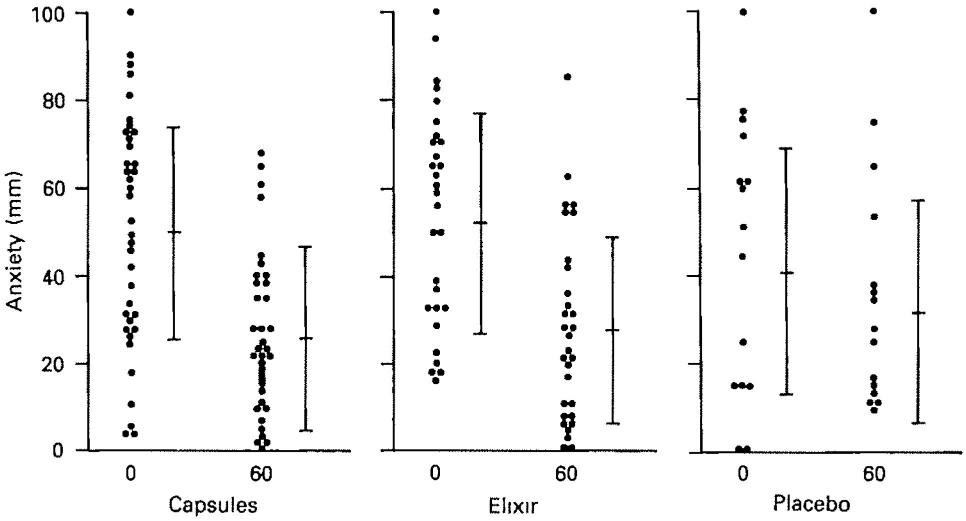

FIG. 3. Mean (SD) anxiety scores using the visual analogue scale before (0) and 60 min (60) after premedication.

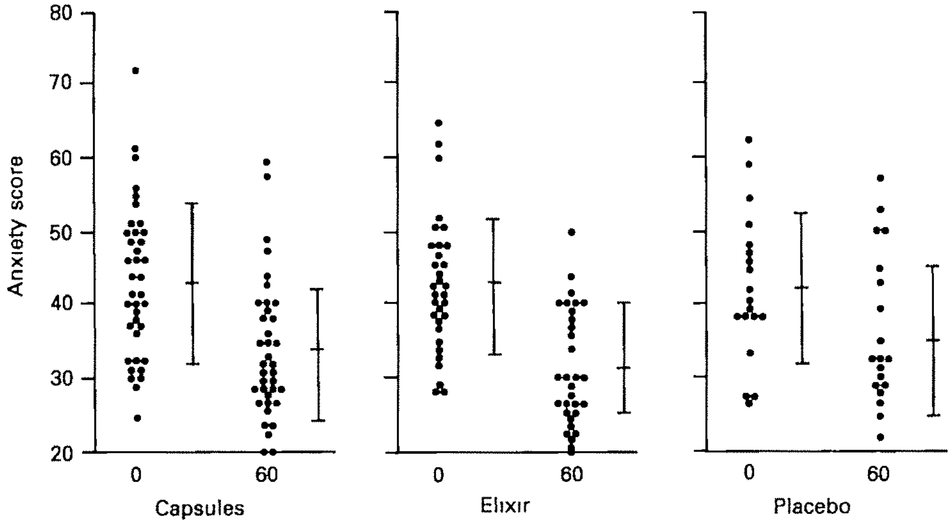

FIG. 4. Mean (SD) anxiety state scores using the Spielberger State Trait Anxiety Inventory before (0) and 60 min (60) after premedication.

"sedated" ratings with concentrations greater than 785 ng ml^{-1}.

TABLE III. *Mean (SEM) plasma concentrations of temazepam associated with sedation scores*

Sedation score	Plasma concn (ng ml^{-1})
Awake	211 (20)
Sleepy	785 (65)
Drowsy	790 (50)
Asleep	940 (85)

DISCUSSION

There was no overall difference in the rate of absorption of temazepam between the two formulations. The time to peak plasma concentration was 30 min, which is shorter than has been found in volunteers (1.6 h [9]). The mean peak plasma concentration of 800 ng ml^{-1} after temazepam 30 mg corresponds well with peak plasma concentrations of around 500 ng ml^{-1} after temazepam 20 mg [9]. Individual variation in peak plasma concentration is seen in volunteers, but a more marked variation in peak plasma concentration and a greater variability in time to peak in preoperative patients has been found in this study. Although there was no statistical difference between the two formulations, there may be less individual variation in those patients given temazepam in elixir form (table II).

Unlike Simpson and Stakes [6], we found that patients with low anxiety trait scores who became highly anxious before operation had peak plasma concentrations of temazepam earlier than patients with anxiety state scores lower than or similar to their trait scores. Our results suggest that high levels of anxiety increase absorption, possibly by hastening gastric emptying, and are more in accordance with the findings of Nakano and colleagues, who described increased plasma concentrations of diazepam in individuals with high neuroticism scores [7].

Although we have been unable to relate anxiolysis with plasma concentration of temazepam, we found a positive correlation between level of sedation and plasma concentration, patients being unsedated at mean plasma concentrations of 211 ng ml^{-1} and sedated at mean concentrations in excess of 785 ng ml^{-1}. This corresponds closely to the finding by Saletu, Gruneberger and Sieghart that deterioration in psychometric performance and sedation occurred at blood concentrations of 250 ng ml^{-1}, and that lesser concentrations were associated with enhanced performance [4].

In order to provide optimal conditions at induction of anaesthesia, it seems reasonable to attempt to achieve moderate sedation and anxiolysis. This study does not identify the concentration required to achieve anxiolysis, but it suggests that a concentration in excess of 200 ng ml^{-1} is needed in order to ensure sedation. This may be achieved more reliably in patients awaiting surgery by giving temazepam in the elixir formulation, which results in less variable absorption. Further studies may be required to elucidate optimal timing of premedication.

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PLASMA CONCENTRATIONS OF BUPIVACAINE AND TWO OF ITS METABOLITES DURING CONTINUOUS INTERSCALENE BRACHIAL PLEXUS BLOCK

P. H. ROSENBERG, P. PERE, R. HEKALI AND M. TUOMINEN

SUMMARY

An interscalene brachial plexus block was performed via a catheter with 20–28 ml of 0.75% bupivacaine plus adrenaline for surgery of the shoulder region in 12 patients. Constant infusion of 0.25% bupivacaine 0.25 mg kg^{-1} h^{-1} was continued for 24 h. During surgery light general anaesthesia, without analgesics, was maintained. Plasma concentrations of total and unbound (free fraction) bupivacaine, desbutylbupivacaine (DBB), 4-hydroxybupivacaine (4-OHB) and alpha$_1$-acid glycoprotein (AAG) were measured at predetermined intervals during the continuous block. The greatest mean plasma concentrations of bupivacaine were measured at 30 min (1.63 (SD 0.55) µg ml^{-1}) and 60 min (1.38 (0.48) µg ml^{-1}). There was a small but statistically significant increase in the plasma concentration of bupivacaine between 12 and 24 h of infusion. The mean unbound concentration of bupivacaine in plasma decreased from 0.044 (0.015) µg ml^{-1} (3.6 (1.1)% of total bupivacaine concentration) at 3 h to 0.023 (0.011) µg ml^{-1} (2.1 (1.0)%) at 24 h. The AAG concentration in plasma increased by 38% in 24 h. The metabolites DBB and 4-OHB were detectable in plasma from 30 min, with a gradual increase during infusion. At 24 h the mean concentrations of DBB and 4-OHB were 0.33 (0.22) µg ml^{-1} and 0.13 (0.04) µg ml^{-1}, respectively. There were no toxic reactions during the blocks.

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques: interscalene brachial plexus block. Biotransformation: bupivacaine. Pharmacokinetics: bupivacaine.

Interscalene brachial plexus block with bupivacaine abolishes pain during and after surgery of the shoulder joint [1–3]. Large doses are used, in general exceeding recommended doses. There is evidence of accumulation of bupivacaine in the circulation, but toxic symptoms are rare and mild, possibly because the concentration of the free (unbound) local anaesthetic remains virtually unchanged in the postoperative period [4, 5]. Hepatic metabolism and elimination of the toxic parent compound may contribute also to the clinical safety of long-term treatment with bupivacaine. Only a small fraction (6%) of i.v. administered bupivacaine is recovered unchanged in the urine of man [6]. The toxicity (LD_{50} i.v. in mice) of the main metabolite, desbutylbupivacaine (2,6-pipecolylxylidine (DBB)) reportedly is about 12.5% of that of bupivacaine [7].

In the study reported here, we have assessed the extent to which the plasma concentration of unbound (active) bupivacaine changes and to what maximum value the concentrations of two bupivacaine metabolites increase during a 24-h interscalene infusion treatment in surgical patients.

PATIENTS AND METHODS

The study was approved by the institutional Ethics Committee and each patient gave informed consent for the study. We studied 12 patients undergoing orthopaedic surgery of the shoulder joint region (table I).

The patients were premedicated with diazepam 0.15 mg kg^{-1} orally, and oxycodone 0.15 mg kg^{-1} i.m. Needle placement for brachial plexus block

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TABLE I. *Patient characteristics. AAG = Alpha$_1$-acid glycoprotein*

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	ASA risk group	Concomitant diseases	AAG concn before op. (g litre^{-1})	Duration of op. (min)
1	M	43	162	78	I	None	0.32	55
2	F	41	172	72	I	None	0.30	65
3	M	53	168	77	III	Angina pectoris	0.12	60
4	M	48	180	74	I	None	0.30	75
5	F	60	152	67	I	None	0.46	65
6	M	44	183	103	I	None	0.62	55
7	M	52	170	67	I	None	0.49	45
8	M	56	174	97	I	None	1.08	50
9	F	49	158	48	I	None	0.24	65
10	M	60	163	83	II	Hypertension	0.29	45
11	F	68	154	55	III	Asthma, diabetes	0.94	85
12	M	48	172	98	II	Severe migraine	0.58	50

via the interscalene approach was aided by use of a nerve stimulator (DualStim, Life-Tech Inc., Houston, Texas) connected to the proximal end of the metal inner needle of a plastic plexus block cannula (Contiplex, B. Braun–Melsungen AG, FRG). For the interscalene brachial plexus block, 20–28 ml (according to the weight of the patient) of 0.75% bupivacaine with adrenaline 5 μg ml^{-1} was injected. Through the plastic plexus block cannula, an interscalene catheter (o.d. 0.85 mm, Contiplex, B. Braun–Melsungen AG, FRG) was introduced and fixed to the skin with a tight suture. Then a local infiltration of the suprascapular nerve (5 ml) and the intercostobrachial nerves (5 ml) was performed with 0.5% bupivacaine. Immediately thereafter, a continuous interscalene infusion of 0.25% bupivacaine 0.25 mg kg^{-1} h^{-1} was continued for 24 h. When all patients had evidence of a developing block by pinprick testing, general anaesthesia was induced. Glycopyrrolate 0.2 mg followed by thiopentone 5 mg kg^{-1} was given i.v. The patient's lungs were ventilated with 1% enflurane in 100% oxygen and then vecuronium 0.1 mg kg^{-1} was given i.v. to facilitate tracheal intubation. General anaesthesia was maintained with 0.2–1% enflurane and 70% nitrous oxide in oxygen. Ringer's acetate solution 3–4 ml kg^{-1} h^{-1} i.v. was given during surgery, and 1–1.5 ml kg^{-1} h^{-1} i.v. in the postoperative period.

Non-invasive arterial systolic and diastolic pressures and heart rates were recorded at 5-min intervals. ECG was monitored continuously in the operating theatre or recovery room, and during general anaesthesia end-tidal $P\text{CO}_2$ and $P\text{O}_2$ were monitored continuously. In all patients the initial neuromuscular block reversed spontaneously during surgery and anticholinesterases were not required.

The distribution of the sensory block (pinprick) and the motor block (flexion at the elbow or wrist) was tested as soon as the patient was co-operative in the recovery room after awakening from general anaesthesia. The patients were observed in the recovery room for about 2 h before transfer to the ward. If a patient complained of postoperative pain in the region operated, oxycodone 0.15 mg kg^{-1} i.m. (0.05–0.06 mg kg^{-1} i.v. in the recovery room) was given. For pain in any other region (e.g. headache, backache) ketoprofen 100 mg per rectum was given. Any side effects were noted on a specifically designed form, by the nurses. Patients were interviewed by one of the investigators at the completion of the 24-h infusion. The catheter was removed and the site of puncture inspected.

Venous blood samples from a contralateral antecubital vein were taken before and 5, 30 and 60 min and 3, 6, 12 and 24 h after induction of the block. Plasma concentrations of bupivacaine and two of its metabolites, desbutylbupivacaine (DBB) and 4-hydroxybupivacaine (4-OHB) were measured in all the samples. The concentration of unbound (free) bupivacaine from samples at 5 min and 3, 12 and 24 h, and the concentration of alpha$_1$-acid glycoprotein (AAG) from samples taken before and 12 and 24 h after induction of the block were also measured.

Bupivacaine and its metabolites were measured by high pressure liquid chromatography [8]. The assay limit for all agents was approximately 0.01 μg ml^{-1}. The coefficients of variation of the intra-assay variability ($n = 12$) of bupivacaine, DBB and 4-OHB were 3%, 5% and 3%, respectively.

Unbound bupivacaine was separated from plasma using an ultrafiltration method (Amicon Micropartition System). The concentrations were corrected for the deviation in test temperature (25 °C) and sample pH (pH 7.75–7.80) from the physiological values using a mean correlation coefficient of 1.14 (SD 0.10). This coefficient was derived from control experiments in which separation of the free local anaesthetic was performed from plasma equilibrated at 37 °C and pH 7.4 (bubbling with 5% carbon dioxide) for 30 min and compared with that at 25 °C and pH 7.75 ($n = 9$).

AAG concentrations in plasma were measured by radial immunodiffusion on M-partigen plates [9] and by an immunoturbidometric method (Kone Process, Finland) with antiserum and standards from Orion Diagnostica (Espoo, Finland).

Statistical analyses

Values are presented as mean (SD). For analysis of differences in concentrations, paired Student's *t* test was used. $P < 0.05$ was considered statistically significant.

RESULTS

The block technique used in this study gave good regional analgesia immediately after surgery in the shoulder region of all patients, except one who had only partial analgesia at the shoulder and the elbow. This patient, however, had a detectable partial motor block of the extremity, similar to that of the other patients. One patient had a vasovagal reaction (bradycardia, hypotension and sweating) during the initial search for the nerve plexus with the nerve stimulator needle. None of the patients required analgesics or additional neuromuscular block during general anaesthesia.

After awakening from general anaesthesia, the patients had either anaesthesia or analgesia of the entire upper extremity in addition to anaesthesia of the shoulder region, except for three patients who had no pinprick analgesia in the region innervated by the ulnar nerve. The catheter was removed accidentally from one patient 9 h after the block. He was given oxycodone i.m. twice in the remaining 15 h.

None of the patients complained of discomfort related to the analgesic therapy during infusion. Toxic symptoms were not observed and the puncture site was not inflamed after infusion. Four patients had signs of Horner's syndrome during the infusion. Another four complained of sore throat.

TABLE II. *Mean (SD) plasma concentrations of total and unbound (free) bupivacaine and alpha$_1$-acid glycoprotein (AAG) during the 24-h interscalene brachial plexus infusion block*

Time	Total bupivacaine (μg ml^{-1})	Unbound bupivacaine (μg ml^{-1})	AAG (g litre^{-1})
0 min	0	0	0.48 (0.29)
5 min	0 82 (0.84)	0 025 (0.020)	
30 min	1 63 (0.55)		
60 min	1.38 (0.48)		
3 h	1 28 (0.41)	0.044 (0.015)	
6 h	1.08 (0.34)		
12 h	0.92 (0 27)	0.029 (0 010)	0.48 (0.24)
24 h	1.08 (0.35)	0.023 (0.011)	0.66 (0.24)

The measured plasma concentrations of bupivacaine, unbound bupivacaine and AAG are shown in table II. Samples up to 6 h only were obtained from the patient whose catheter was removed inadvertently after 9 h of infusion.

There was great interindividual variation in both total and unbound plasma concentrations of bupivacaine. The greatest individual concentration of bupivacaine was 3.25 μg ml^{-1} (unbound 0.072 μg ml^{-1}) occurring in patient No. 8, 5 min after the initial interscalene injection. This particular patient had the greatest individual plasma concentrations of bupivacaine throughout the period of observation. His unbound bupivacaine concentration decreased from 0.072 μg ml^{-1} (2.2% of total bupivacaine concentration) at 5 min to 0.019 μg ml^{-1} (1.2% of total bupivacaine concentration) at 24 h, while his AAG concentration increased from 1.08 g litre^{-1} to 1.22 g litre^{-1}.

In the other patients, the maximal plasma concentration of bupivacaine was measured at 30 or 60 min. There was a small but significant increase in the concentration of bupivacaine between 12 (0.92 (0.27) μg ml^{-1}) and 24 h (1.08 (0.35) μg ml^{-1}) ($P < 0.01$). The fraction of unbound bupivacaine, on average, was unchanged during the first 3 h of infusion, but decreased thereafter from 3.6 (1.1)% (0.044 (0.015) μg ml^{-1}) to 2.1 (1.0)% (0.023 (0.011) μg ml^{-1}) during the remaining 21 h ($P < 0.001$). The greatest indiv-

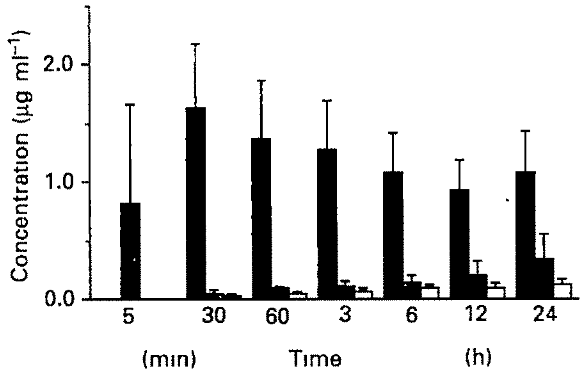

FIG. 1. Mean plasma concentrations of bupivacaine (■), desbutylbupivacaine (■) and 4-hydroxybupivacaine (□) during continuous interscalene brachial plexus block in surgical patients.

idual concentration of unbound bupivacaine at 24 h was 0.051 μg ml^{-1} (total 1.27 μg ml^{-1}).

The mean plasma concentration of AAG increased from 0.48 (0.29) g $litre^{-1}$ at the beginning of the bupivacaine infusion to 0.66 (0.24) g $litre^{-1}$ during the 24 h ($P = 0.15$). Only in one patient (No. 11) was there a small decrease in AAG, from 0.94 g $litre^{-1}$ to 0.85 g $litre^{-1}$.

Measurable plasma concentrations of DBB and 4-OHB were present 30 min after the initial interscalene injection of bupivacaine. The concentrations of both metabolites increased gradually, more so in the case of DBB (fig. 1). At 24 h the mean concentrations of DBB and 4-OHB were 0.33 (0.22) μg ml^{-1} and 0.13 (0.04) μg ml^{-1}, respectively. The greatest individual DBB concentration at 24 h was 0.86 μg ml^{-1} (total bupivacaine 1.27 μg ml^{-1}).

DISCUSSION

This study confirms previous clinical observations that continuous interscalene infusion of bupivacaine for therapeutic relief of postoperative pain (500–800 mg 24 h^{-1}) is not likely to cause toxic complications [1, 2]. This view is shared by others who have investigated continuous extradural analgesia with bupivacaine and found no toxicity, despite relatively great concentrations of bupivacaine in plasma [10] and relatively slow accumulation of bupivacaine in blood during repeated intermittent administration [11].

The main reason for the lack of toxicity is the unchanged [4, 5], or even decreasing concentration of free bupivacaine in plasma. As predicted [2], surgery of the shoulder stimulated acute-phase protein synthesis: the AAG concentration increased by approximately 38 %, on average, in 24 h. The AAG concentrations may continue to increase until 5 days after surgery [12], allowing increased binding of bupivacaine in plasma. In our patients, administration of bupivacaine by continuous infusion with the same dosage could, therefore, have been extended safely beyond 24 h. The concentrations of unbound bupivacaine in plasma at 24 h were considerably less than the estimated plasma concentration of unbound bupivacaine which may produce toxic central nervous system symptoms in cancer patients during continuous extradural infusion (0.24 μg ml^{-1}) [13].

The plasma concentrations of AAG before surgery in otherwise healthy surgical patients may be difficult to predict. Despite the lack of known AAG reducing factors, such as liver disease, nephrotic syndrome and young age, etc., or factors which increase the concentration of AAG, such as trauma and cancer [14], the concentrations of AAG before operation in our patients exhibited a wide range (0.12–1.08 g $litre^{-1}$).

In addition to extensive binding to plasma protein, hepatic metabolism may inhibit bupivacaine activity. In comparison with lignocaine (0.65), the hepatic extraction ratio of bupivacaine in man is relatively small (0.38) [15]. However, hepatic blood flow and splanchnic extraction (0.80) in man have been shown to increase markedly when a constant i.v. infusion of bupivacaine 2 mg min^{-1} is given [16], resulting in a high hepatic clearance of bupivacaine at the beginning of the infusion. The splanchnic extraction ratio decreased to about 50 % in 2.5 h during the infusion. In the case of amide-type local anaesthetics, hepatic clearance and metabolic clearance are virtually interchangeable terms [17] and, therefore, the hepatic metabolism of bupivacaine may offer another protective mechanism against toxicity when large doses are used in patients with normal liver function.

Only about 6 % of a bolus dose of bupivacaine is excreted unchanged, and about 5 % appears as desbutylbupivacaine in urine collected for 24 h in man [6]. As almost 50 % of an i.v. dose of desbutylbupivacaine is excreted unchanged in urine [6], the amount of desbutylbupivacaine formed by hepatic metabolism of bupivacaine is probably relatively small. However, as shown in the present study, the urinary elimination is not rapid enough to prevent considerable cumulation of desbutylbupivacaine in blood when bupivacaine is administered as a continuous infusion. Further metabolic degradation of desbutylbupivacaine by amide hydrolysis may be inhibited by steric interference from the piperidine ring of the molecule [18]. Although it has been suggested that desbutylbupivacaine is pharmacologically inactive [19], its LD_{50} value (i.v. in mice) of 63 mg kg^{-1} [7], implies that this is not so. For comparison, the LD_{50} (i.v. in mice) of bupivacaine and mepivacaine are 7.8 mg kg^{-1} and 40 mg kg^{-1}, respectively [20]. As the desbutylbupivacaine molecule represents the basic structure and one of the main metabolites of a series of pipecolylxylidide-based local anaesthetics (mepivacaine, ropivacaine, bupivacaine), it would not be surprising to find some local anaesthetic properties in desbutylbupivacaine.

The toxicity of 4-hydroxybupivacaine is not known, but this hydrophilic metabolite is probably conjugated extensively and excreted by the kidneys. Less than 1 %, on average, of an i.m. dose of bupivacaine was recovered as 4-hydroxybupivacaine in urine over a period of 24 h [21].

The role played by each of the metabolic pathways and the pharmacological and toxicological actions of the metabolites of bupivacaine warrant further study. Because of great species variation in metabolic pathways [18, 22], animal data may probably not be applicable directly to man.

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COMPARISON OF EXTRADURAL ROPIVACAINE AND BUPIVACAINE

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SUMMARY

Ropivacaine, a new long acting amide type local anaesthetic, was compared with bupivacaine in a randomized double-blind study. One hundred and ten patients undergoing extradural anaesthesia received a test dose of 3 ml of 1% lignocaine with adrenaline which was followed by 15 ml of one of five solutions: 0.5, 0.75 or 1.0% ropivacaine or 0.5 or 0.75% bupivacaine. There was little difference between the groups with respect to speed of onset or sensory block. The duration of analgesia was increased by increasing the concentration of both drugs, but this had minimal effect on onset time or extent of block. When the same concentration of each drug was administered, there were inconsistent differences in duration of sensory block, none of which was statistically significant. Increasing concentration of both drugs resulted in greater degree and longer duration of motor block. Ropivacaine produced a slower onset, shorter duration and less intense motor block than the same concentration of bupivacaine. The cardiovascular changes were similar in all groups.

KEY WORDS

Anaesthetic techniques extradural Anaesthetics, local ropivacaine, bupivacaine

Ropivacaine (S-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate) is a new, long acting, amide type local anaesthetic agent which has a chemical structure similar to that of bupivacaine, the butyl group being replaced by a propyl group [1]. It also differs in that it is prepared as the S isomer rather than as a racemic mixture. Ropivacaine is less lipid soluble than bupivacaine and *in vitro* comparisons [1, 2] have shown it to be slightly less potent. However, *in vivo* animal studies have suggested that the central administration of both drugs produces similar patterns of onset and extent of sensory block, but that ropivacaine has a shorter duration of action [3] and causes less motor block [4]. The vasoconstrictor properties of ropivacaine [5] were perhaps responsible for the longer duration of action seen when it was used for infiltration or peripheral nerve block [3, 5, 6].

In man, ropivacaine has been used successfully for both brachial plexus [7] and extradural block [8, 9]. These open studies indicated that the drug produced effective analgesia and that motor block appeared to regress considerably more rapidly than sensory. The duration of sensory analgesia provided by ropivacaine has been shown to be increased with greater concentration [9]. In addition, ropivacaine at similar plasma concentrations has been shown to be less cardiotoxic than bupivacaine in both animals [10] and man [11]. Thus ropivacaine would have a better therapeutic ratio, if the drugs are of equivalent potency. This study was designed to provide a double-blind comparison of ropivacaine with bupivacaine in extradural block.

PATIENTS AND METHODS

After Ethics Committee approval, we studied 120 patients (ASA I–II, ages 18–70 yr) undergoing elective urological, gynaecological, orthopaedic or

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varicose vein surgery under extradural block. After giving written, informed consent the patients were allocated randomly in a double-blind manner to one of the following five groups:

0.5 % Ropivacaine 15 ml (75 mg)
0.75 % Ropivacaine 15 ml (112.5 mg)
1.0 % Ropivacaine 15 ml (150 mg)
0.5 % Bupivacaine 15 ml (75 mg)
0.75 % Bupivacaine 15 ml (112.5 mg)

A series of boxed coded ampoules was used, so that each solution group contained similar numbers of patients undergoing each type of surgery and so that each anaesthetist performed the same number of blocks with each test solution.

The patients were premedicated with temazepam 10 mg orally approximately 1 h before anaesthesia. I.v. administration of fluids was restricted to a maximum of 250 ml before operation. With the patient in the lateral position, the skin over the 3rd (or 2nd) lumbar interspace was infiltrated with 1 % lignocaine and the extradural space located with a 16-gauge Tuohy needle using midline loss of resistance to saline injection. An end-hole catheter was inserted 3 cm in a cephalad direction. After negative aspiration for blood and CSF, a test dose of 3 ml of 1 % lignocaine with adrenaline 1:200000 was injected and the catheter flushed with saline 2 ml. The patient was then turned supine. Five minutes after the test dose, in the absence of any adverse sequelae, 15 ml of the study solution was injected at 0.33 ml s^{-1} with a 45-s pause between each 5 ml, so that the total injection time was 2 min 15 s. Surgery was not commenced until at least 30 min after injection. Sedation with propofol or midazolam, or general anaesthesia (usually with propofol and enflurane and nitrous oxide in oxygen), were used if desired or required.

All assessments were related to the end of injection of the study solution (time zero). The height of sensory block was assessed on the right side using analgesia to pinprick with a 27-gauge short-bevelled dental needle. Lower limb motor block was recorded using a modified Bromage scale (0 = able to straight leg raise, full flexion of knees and feet; 1 = inability to raise leg, able to flex knees; 2 = inability to flex knees, able to flex ankles; 3 = inability to flex ankles). Assessments were made at 2, 5, 10, 15, 20, 25 and 30 min and every 30 min thereafter until the block had regressed completely, unless sedation, anaesthesia or restricted access during surgery prevented it. If assessments were precluded during surgery, one was performed as soon as possible after the end of the procedure. The patient's arterial pressure and heart rate were recorded also at the time of each assessment for the first 3 h. Analgesia and muscle relaxation during surgery were judged as satisfactory or unsatisfactory. If the patients experienced any discomfort or moved their limbs so as to interfere with surgery, the blocks were deemed unsatisfactory. If there were any obvious technical problems with the extradural injection, the patient was excluded and another recruited to the same study group; the double-blind nature of the trial was maintained.

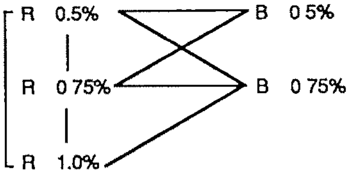

FIG. 1 The multiple group analysis: eight pairwise comparisons. B = bupivacaine; R = ropivacaine.

Eight pairwise comparisons were performed (fig. 1) using the non-parametric techniques of Wilcoxon rank sum and Fischer's exact test as appropriate. To compensate for the multiple comparisons, a sequentially rejective Bonferroni–Holm method [12] was used. This involved arranging the P values for each comparison in order and relating them to the Bonferroni–Holm rejection criteria, which for a significance of 5 % are: 0.00625, 0.0071, 0.0083, 0.010, 0.0125, 0.017, 0.025 and 0.05. The smallest value of P was considered to be significant if it was less than or equal to 0.00625. If the first was significant, the next smallest value was deemed significant if it was less than 0.0071, and so on until one value was insignificant.

A further stratified analysis using Wilcoxon rank sum test for stratified data (a test that does not presume parallel dose–response curves) was performed. This analysis involved combining the data for the 0.5 % and 0.75 % groups of each drug and comparing ropivacaine with bupivacaine ($P < 0.05$ considered significant). Two-tailed tests were used.

RESULTS

The groups were similar in regard to age, weight, height or gender (table I). In addition to the 110 valid study entries, a further 10 patients were

TABLE I. *Patient characteristics (mean (SD)), maximum block heights and unsatisfactory blocks (in terms of either analgesia (Analg.) or muscle relaxation (Relax.) and numbers requiring general anaesthesia (GA))*

	Ropivacaine			Bupivacaine	
Group	0.5%	0.75%	1.0%	0.5%	0.75%
Age (yr)	55 (11)	51 (14)	48 (14)	48 (14)	49 (14)
Weight (kg)	69 (10)	74 (13)	72 (9)	68 (12)	72 (14)
Height (cm)	169 (10)	171 (9)	170 (8)	169 (10)	171 (11)
Sex (F:M)	14:8	9.13	10:12	10:12	11:11
Maximum block heights					
Mean (SD)	T6 (3)	T6 (5)	T6 (3)	T6 (3)	T6 (4)
Median	T6	T6	T6	T5	T5
Range	T11–T2	L1–C3	T11–C3	T11–C8	T12–C4
Unsatisfactory blocks (*n*/22)					
Number	8	4	1	3	4
Analg.	7	2	1	3	4
Relax.	1	2	1	0	0
GA	3	0	0	2	1

TABLE II. *Exclusions on technical grounds*

Group	*n*	Reason
Ropivacaine		
0.5%	3	I.v. injection Paravertebral injection Anatomical abnormality
0.75%	2	I.v. injection Paravertebral injection
1.0%	0	
Bupivacaine		
0.5%	4	Two i.v. injection Paravertebral injection Anatomical abnormality
0.75%	1	Paravertebral injection

excluded for several technical reasons (table II) after they had given informed consent. The programme did not allow continued inclusion in the study when such an event had occurred.

Multiple group analysis

Sensory block. All five solutions produced rapidly effective extradural block. There were no significant differences between the groups with regard to onset time at any dermatomal level (table III, fig. 2). The mean upper level of block was T6 in each group, but the range of blocks was very wide (table I).

There was a tendency towards a longer duration of sensory block at most dermatomal levels with increasing concentration of both drugs. This reached statistical significance when 0.75% and 1.0% ropivacaine were compared with 0.5% at L5 and S1, and T12–S5, and when 0.75% bupivacaine was compared with 0.5% ropivacaine between T12 and S1 (table III, fig. 2).

Motor block. Onset of level 2 motor block was significantly faster with 0.75% bupivacaine than with 0.5% or 0.75% ropivacaine and there was a tendency towards more intense motor block with bupivacaine and with increasing concentration of each drug (table III). This was significant when 1.0% ropivacaine was compared with 0.5% at motor block level 3.

There was also a tendency towards increased duration of motor block with increasing concentration of each drug and with bupivacaine compared with ropivacaine. However, statistical significance was obtained only when level 1 block with 0.75% bupivacaine was compared with 0.5% ropivacaine (table III).

Stratified analysis

At T12, but at *no* other level, ropivacaine had a significantly slower onset ($P = 0.01$) and shorter duration ($P = 0.015$) of sensory block. Ropivacaine had a slower onset of levels 1 and 2 motor block ($P = 0.006$ and 0.001, respectively), less intense degree of motor block after 30 min ($P = 0.013$), and shorter duration of motor block

TABLE III. *Numbers* (n *of 22*) *of patients achieving sensory block and mean* (SD) *onset and duration times, at S1, L1 and T6. Numbers* (n *of 22*) *of patients achieving levels 1, 2 or 3 motor block and mean* (SD) *onset and duration times.* $^*P < 0.00625$

	Ropivacaine			Bupivacaine	
Group	0.5%	0.75%	1.0%	0.5%	0.75%
Sensory block					
S1					
No.	21	22	22	21	21
Onset (min)	13 (10)	11 (6)	16 (14)	10 (5)	12 (7)
Duration (min)	235 (46)	308 (70)	327 (106)	266 (100)	326 (87)
L1					
No.	22	22	22	22	22
Onset (min)	8 (4)	8 (9)	6 (3)	6 (5)	6 (5)
Duration (min)	210 (53)	272 (96)	322 (84)	266 (100)	324 (83)
T6					
No.	11	12	13	13	15
Onset (min)	20 (10)	12 (5)	23 (15)	12 (7)	18 (13)
Duration (min)	161 (50)	192 (92)	153 (61)	129 (55)	179 (89)
Motor block					
Level 1					
No.	10	6	3	6	3
Onset (min)	20 (19)	26 (25)	14 (7)	16 (9)	12 (5)
Duration (min)	148 (62)	190 (85)	240 (97)	194 (56)	263 (80)
Level 2					
No.	5	6	6	9	6
Onset (min)	39 (16)	44 (28)	39 (34)	26 (15)	21 (9)
Duration (min)	120 (50)	140 (82)	189 (74)	156 (59)	217 (69)
Level 3					
No.	2*	7	12*	4	10
Onset (min)	105 (21)	74 (42)	68 (37)	79 (51)	96 (57)
Duration (min)	60 (–)	119 (54)	136 (66)	124 (72)	154 (65)

at levels 1 and 2 ($P = 0.001$ and 0.003, respectively) than bupivacaine.

Miscellaneous results

Cardiovascular effects. The cardiovascular changes in the first 30 min were similar in all groups and were of the order expected with the block heights achieved. Generally, the systolic, diastolic and mean arterial pressures decreased by about 20% from baseline values over the first 20 min, whereas the heart rate tended to increase over the first 15 min and thereafter decrease to slightly less than the baseline figure. There were no significant differences between any of the five groups in the five cardiovascular variables recorded.

Quality of block. Subjective assessment of the suitability of the blocks for surgery revealed no significant differences between the groups, but there were more unsatisfactory blocks and general anaesthetics required with 0.5% ropivacaine (table I).

Plasma concentrations. Peripheral venous blood samples were taken from four patients (all exclusions) after suspected i.v. administration of the study drug. Ropivacaine base was determined in plasma using gas chromatography and a nitrogen sensitive detector at Astra Pain Control AB, Sodertalje, Sweden (Monica Bjork) (table IV).

Side effects. There were similar numbers of minor side effects in each group, the commonest being backache, which was reported spontaneously by 26 patients (23%) when questioned the day after anaesthesia. For the purposes of this study, bradycardia was defined as a decrease in heart rate warranting treatment, rather than an arbitrary value. The overall incidence was 8.2%, with no significant differences between groups. Nausea was reported by 14% of the patients, of whom 2% also vomited. Among the patients who did not have a urinary catheter for surgical reasons, there were only two cases of urinary retention requiring such intervention.

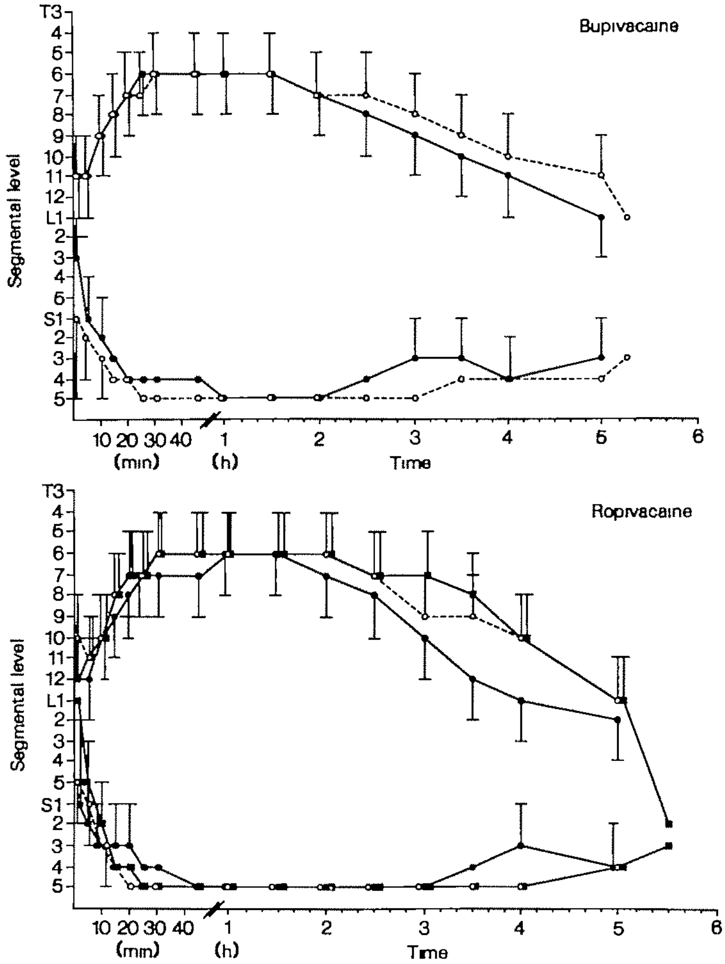

FIG. 2 Segmental spread of analgesia (mean, 1.96 SEM) of 0.5% (●), 0.75% (○) and 1.0% (■) ropivacaine, and 0.5% (●) and 0.75% (○) bupivacaine.

TABLE IV. *Plasma concentrations of local anaesthetic in four patients in whom accidental i.v. administration was suspected. Drug administered, and time of withdrawal of sample*

Patient No.	Drug	Time (min)	Plasma concn (mg litre^{-1})
15	0.5% Ropivacaine 10 ml	6	1.09
		20	0.75
77	0.75% Ropivacaine 15 ml	14	3.70
		30	1.82
		60	1.26
		90	1.12
80	0.5% Bupivacaine 10 ml	2	2.00
		9	1.55
		15	1.51
96	0.5% Bupivacaine 15 ml	6	2.04
		30	1.05

DISCUSSION

We have confirmed that ropivacaine administered extradurally was an effective long acting local anaesthetic. The duration of sensory block was similar to that produced by the same concentration of bupivacaine and the results have confirmed those obtained in a previous open study [9]. There were no significant differences in duration of sensory block at any dermatomal level when equal concentrations of the two drugs were compared. There was a significant prolongation of sensory block with bupivacaine ($P = 0.015$) at the T12 dermatome, but at no other level, when the pooled data for both drugs were compared. Duration of analgesia was increased, frequently significantly, with increasing concentration of both drugs.

The multiple group comparisons revealed that the speed of onset of analgesia was similar in all groups, at all dermatomal levels. The onset times were similar also after stratified analysis of the data, although that for bupivacaine was significantly faster at one level (T12). The mean maximum block height was the same in all five groups—a somewhat surprising finding, in view of the differences in dose and concentration of drug used. This result conflicts with that of the open study [9] in which after the injection of 20 ml of solution, it was found that the maximum height was significantly lower with 0.5% ropivacaine than with 0.75 or 1.0%.

The present study has also provided further evidence that ropivacaine produces a greater degree of differential block than bupivacaine. This is in keeping with *in vitro* prediction [1] and early animal and clinical work [3, 4, 9]. The motor block produced by ropivacaine was slower in onset, shorter in duration and less intense. The degree of motor block and its duration increased with concentration of both drugs, although onset times were not significantly different.

Analysis of the quality of block revealed no significant differences between the groups, although the 0.5% ropivacaine group had more unsatisfactory blocks than the others. Despite the random allocation, the average duration of surgery was longer in this group than in any other except 0.75% ropivacaine, a factor which may explain the finding. There were also more knee replacement patients in the 0.5% ropivacaine group who, because of the duration of the procedure and the use of a tourniquet, experienced more unsatisfactory blocks.

The plasma concentrations of drug in the four patients in whom i.v. injection was suspected were consistent with such an event, although not at a level that would cause concern. This promotes two observations. First, that the injection of 3 ml of 1% lignocaine with adrenaline did not provide unequivocal evidence of i.v. catheter placement in any case; and second that the slow, incremental injection technique used for the main dose did indicate that i.v. injection had occurred without harming the patient. This method may thus be preferable to the use of a test dose.

In conclusion, the results of this study confirm the suitability of ropivacaine for extradural anaesthesia in man. It appears to induce a sensory block similar to that obtained with bupivacaine, although perhaps with a slightly shorter duration of action. The motor block induced by ropivacaine was less than that of bupivacaine—a finding which, when combined with its known lesser cardiotoxicity, makes ropivacaine a drug worthy of continued investigation. The finding that the rate of onset and extent of sensory block were the same in all groups was surprising in view of the range of drug and dose used. The prior administration of a small dose of lignocaine may have influenced the onset particularly, and obscured any differences. There is a need for a comparison of the two drugs in the absence of such prior medication.

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UNEXPECTED, DIFFICULT LARYNGOSCOPY: A PROSPECTIVE SURVEY IN ROUTINE GENERAL SURGERY

K. N. WILLIAMS, F. CARLI AND R. S. CORMACK

SUMMARY

A prospective study of unexpected, difficult laryngoscopy was carried out. During a 7-month period, all general surgery patients in whom the trachea was intubated were assessed; only those with obvious neck pathology were excluded. Ease or difficulty of laryngoscopy was graded by a standard method. There were no grade 4 cases and no failed intubations in a total of 1387 cases. There were significant differences in the results recorded by different individuals; this did not correlate with seniority or with the type of surgery. Four factors have been identified which help to explain these discrepancies. These findings are analysed in relation to the training of junior staff, with particular reference to obstetric anaesthesia.

KEY WORDS

Intubation, tracheal. complications, technique, training

Difficulty in tracheal intubation is known to be the main factor in deaths associated with anaesthesia in young patients. It has been the subject of many studies, but a puzzling feature of this work is the enormous variation in the reported frequency of difficult laryngoscopy, ranging from 1 in 8 [1] at one extreme, to 1 in 300 [2] at the other. Our initial aim was to identify the reasons for these discrepancies.

Diseases which are notorious for causing difficulty with tracheal intubation, such as Still's disease and ankylosing spondylitis, do occur in obstetric patients, but in general they do not cause disaster. Only once have these diseases been implicated in the 30 years covered by the Confidential Enquiries. Such patients are easy to identify in advance and appropriate measures are taken to avoid trouble; it is the unexpected difficulty in a patient with no neck pathology that causes disaster. Because of this, patients with obvious neck pathology were excluded from this study.

PATIENTS AND METHODS

Anaesthetists were asked to rate difficulty of laryngoscopy into one of four grades, using the method we described previously [3]. A copy of this scheme was displayed in each anaesthetic room (fig. 1). The grade was entered in the theatre records and for most patients that was the only information noted. However, if there was any difficulty with laryngoscopy, full details were recorded. The data were transferred to a microcomputer for analysis.

The compliance rate was mostly about 90%, but this decreased to 77% during busy periods, when there was a tendency for easy cases to go unrecorded. Thus the total for grade 1 are about 15% too low, but this does not materially affect our conclusions.

RESULTS

Table I shows all the data. A χ^2 test for R × C contingency on table I approached significance ($P = 0.07$), but the proportion of cells with expected frequency (E) less than 5 was high (70%), which makes χ^2 unreliable. To rectify this, rows and columns were amalgamated, as advocated by Armitage [4], to produce table II: all rows with a row total of 5 or less were pooled (that is, individuals who performed five or fewer intubations in the study period were put in one group); columns 1 and 2 (the easy cases) were amalgamated; and columns 3 and 4 (the difficult cases) were amalgamated. Apart from statistical

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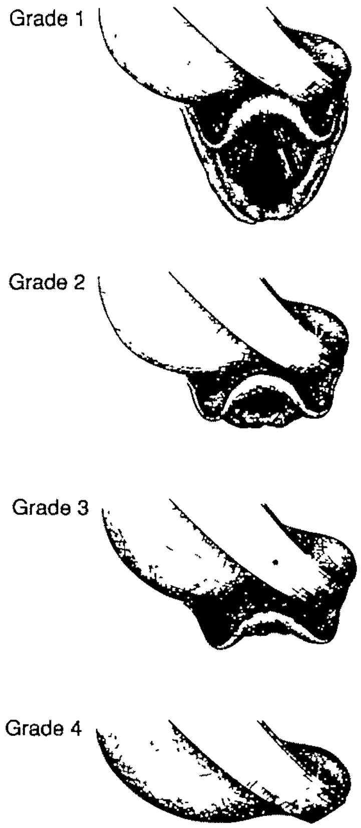

FIG. 1 Grading difficulty of laryngoscopy. It is assumed that care has been taken to get the best possible view of the vocal cords.

TABLE I. *Incidence of each grade of difficulty of laryngoscopy recorded by individual participating anaesthetist.* † *Beginner*

	Grade of laryngoscopy				
Rank of anaesthetist	1	2	3	4	Totals
Consultant	75	15	2	0	92
	84	4	2	0	90
	70	6	1	0	77
	58	9	2	0	69
	52	9	5	0	66
	36	3	0	0	39
	29	5	1	0	35
	13	2	0	0	15
	14	0	0	0	14
	11	0	3	0	14
	3	1	0	0	4
Clinical Assistant	20	2	1	0	23
Senior Registrar	73	20	5	0	98
	61	4	5	0	70
	27	1	1	0	29
	15	1	0	0	16
	4	1	0	0	5
Registrar	38	7	1	0	46
	35	6	1	0	42
	19	2	2	0	23
	18	3	1	0	22
	17	3	0	0	20
	13	2	2	0	17
	11	0	0	0	11
	9	0	0	0	9
	7	0	0	0	7
	3	0	0	0	3
	1	0	0	0	1
Senior House Officer	78	2	0	0	80
	72	8	0	0	80
	70	2	0	0	72
	65	5	2	0	72
	54	7	1	0	62
	17	8	0	0	25
	12	0	1	0	13†
	11	1	0	0	12†
	7	1	3	0	11†
	3	0	0	0	3
Totals	1205	140	42	0	1387

benefits, table II is more relevant clinically than table I; in effect it emphasizes the ratio of difficult to easy cases reported by each individual.

Amalgamating rows and columns in table II reduced the number of cells with $E < 5$ from 70% to 50%. This is still larger than the recommended maximum of 20%, therefore it seemed advisable to cross-check against a computer simulation, as advocated for controversial cases [5]. Table III shows what would happen if the null hypothesis were true and our trial were repeated 12000 times. The marginal totals were fixed, as in table II, but the body of the table varied randomly. It can be seen (table III) that a small amount of probability has migrated from the middle of the distribution into the tail, but in general the experimental *P* values match the theoretical ones quite well. This adds weight to previous evidence [6,7] that χ^2 provides a better approximation than was thought in the past. Only 2% of simulated trials produced a χ^2 greater than 54.7 (table III), so the real trial value of 71.3 (table II) can hardly have been produced by random variation.

Having established that these were real differences, we tried next to identify the cause. The distribution of difficult cases was unrelated either to seniority of the individual or to the type of surgery (table IV). The last step was to go back to table II and examine the results of each an-

TABLE II. *Data from table I summarized to highlight the ratio of easy:difficult laryngoscopies seen by each anaesthetist: Grades 1+2 = easy cases; grades 3+4 = difficult cases. Mixed rank = pooled data for those who performed a total of five or fewer laryngoscopies.* $\chi^2 = 71.33$ *with 33 degrees of freedom;* $P < 0.0001$. *** Contribution to* $\chi^2 > 15.0$; ** Contribution to* $\chi^2 > 4.0$

Rank of anaesthetist	Grade of laryngoscopy 1+2	3+4	Totals
Consultant	90	2	92
	88	2	90
	76	1	77
	67	2	69
	61	5*	66
	39	0	39
	34	1	35
	15	0	15
	14	0	14
	11	3**	14
Clinical Assistant	22	1	23
Senior Registrar	93	5	98
	65	5	70
	28	1	29
	16	0	16
Registrar	45	1	46
	41	1	42
	21	2	23
	21	1	22
	20	0	20
	15	2*	17
	11	0	11
	9	0	9
	7	0	7
Senior House Officer	80	0	80
	80	0	80
	72	0	72
	70	2	72
	61	1	62
	25	0	25
	12	1	13
	12	0	12
	8	3**	11
Mixed Rank	16	0	16
Totals	1345	42	1387

aesthetist. Four individuals contributed more to χ^2 than the remainder—they had abnormally high incidences of difficult laryngoscopy (mean incidence overall 3%): 27% and 21% for two (one a consultant, the other an S.H.O.), and 12% and 8% for two others (one a consultant, the other a trainee).

DISCUSSION

Difficult laryngoscopy vs *difficult intubation*

TABLE III. *Verification of the statistics of table II using computer simulations [7]. This shows what would happen if the null hypothesis were true and our trial were repeated 12000 times. The experimental* χ^2 *values followed the* χ^2 *distribution quite well, despite many cells with expected values of* < 5. *Only 2% of trials made* $\chi^2 > 54.7$, *so the value of 71.3 in table II cannot be ascribed to random variation*

χ^2	Predicted *P*	Experimental *P* (95% confidence limits)
> 32.3	0.502	0.473 (0.464–0.481)
> 38.1	0.250	0.244 (0.238–0.250)
> 43.7	0.100	0.115 (0.109–0.121)
> 47.4	0.050	0.070 (0.065–0.074)
> 54.7	0.010	0.023 (0.020–0.025)

TABLE IV. *Negative findings. There was no evidence that the distribution of difficult cases was related to the seniority of the anaesthetist* ($\chi^2 = 6.18$; $df = 4$; $P = 0.19$) *or to the type of surgery* ($\chi^2 = 3.14$; $df = 4$; $P = 0.53$)

	Grade of laryngoscopy 1+2	3+4	Totals
Rank of anaesthetist			
Consultant	499	16	515
Clinical Assistant	22	1	23
Senior Registrar	207	11	218
Registrar	194	7	201
Senior House Officer	423	7	430
Totals	1345	42	1387
Type of surgery			
General surgery	495	12	507
Genito-urinary surgery	63	4	67
Orthopaedics	364	11	375
Gynaecology	320	12	332
Vascular	103	3	106
Totals	1345	42	1387

To avoid confusion, a distinction should be drawn between difficult laryngoscopy and difficult intubation. If the cords cannot be seen (grade 3 or 4), this is described reasonably as difficult laryngoscopy, but it may not necessarily be a difficult intubation. Many grade 3 patients have a trachea which may be intubated at a first attempt, even by a comparative novice. Difficult tracheal intubation is much harder to define. It depends on the skill of the individual, so that any survey of its frequency depends greatly on the dexterity of those involved; variable results are inevitable.

By contrast, difficult laryngoscopy, as defined above, should be more objective. The four requirements for gaining the best view are well known: head in the Magill position, good relax-

TABLE V. *Surveys of the incidence of difficult laryngoscopy in routine general surgery*

Source	Grades 3+4	*n*	Incidence	95% confidence limits
Mallampati et al. [1]	28	210	1:8 (13%)	1:5–1:11
Cohen, Laurito and Segil [9]	48	665	1:14 (7%)	1:11–1:19
Present study	42	1387	1:33 (3%)	1:25–1:46
Wilson et al. [8]	12	778	1·65 (1.5%)	1:37–1 126
Bellhouse and Doré [2]	13	3800	1:292 (0.3%)	1:171–1:551

ation, firm forward traction on the laryngoscope and, if necessary, firm backward pressure on the cricoid. All these are easy manoeuvres, so a beginner should obtain the same view as an expert. The novice may take longer, but should obtain the same result, provided s/he follows instructions. It has been suggested that exact positioning of the blade tip is crucial, but watching different anaesthetists raises doubts on this point. Typically, the expert gives the grade within seconds—it is the beginner who takes a long time trying different positions of the blade, usually with no improvement in the view of the larynx.

Thus our original hope was that the laryngoscopy grades would provide a reproducible measure, largely independent of the skill of those involved, but the surveys published so far have conspicuously failed to bear this out (table V).

The difference apparent in table V is too big to be fortuitous—most of the confidence limits do not overlap. Were the populations different? Mallampati and colleagues [1] stated that no patient had significant neck pathology. Bellhouse and Doré [2] described 19 patients in whom laryngoscopy was difficult; six had arthritis of the neck, but they have been excluded from the calculations in table V. Thus there is no reason to think there was any real difference between the populations studied; the difference must lie in the techniques used for laryngoscopy.

Analysis of laryngoscopic techniques

In the Results section it was observed that there were very large differences between the results reported by different anaesthetists, not accounted for by seniority or by type of surgery.

On enquiry, one consultant stated that when he encounters a grade 3 patient, which he knows from past experience has been an easy tracheal intubation, he makes no special effort to see the cords, but intubates blind, using the Macintosh method. This has the benefit of maintaining practice with blind intubation, which otherwise is seldom needed.

Another consultant commented that he normally intubates the trachea without full relaxation, but added that, in emergency cases, he would use suxamethonium to obtain total paralysis and would expect to see fewer grade 3 patients. These two factors account for the unexpectedly high incidence of grade 3 reported by some senior anaesthetists.

A third, new, factor was inadequate traction on the laryngoscope. One patient, rated grade 4 initially, was found to be grade 3 by a second anaesthetist, who intubated the trachea without difficulty. Three similar cases occurred in recent years at this hospital [unpublished observations]. The common factor was that the anaesthetist, although different in each case, was small, with thin wrists, whilst the patient was large and heavy. Those who came to help commented that more than normal traction was needed to see the vocal cords. Once identified, the problem is solved easily; for example, the assistant may be asked to apply additional traction on the handle of the laryngoscope. One reason for inadequate traction is concern about possible trauma. When intubation has required more force than normal, the patient should be seen the next day; it is reassuring to find how rarely any complaint of sore throat is elicited.

A fourth source of variation was technical error. A novice may reach the stage of giving anaesthetics unsupervised without having grasped the fact that a grade 3 view sometimes changes to grade 1 merely on institution of cricoid pressure. Cricoid pressure, applied incorrectly, may make laryngoscopy more difficult. Forward traction on the laryngoscope may be counteracted by backward pressure on the larynx, if applied too high up. In doubtful cases the anaesthetist, while performing the laryngoscopy with his left hand, should apply cricoid pressure with his right hand. Having found that position which gives the best view, the assistant should be asked to press on the same spot. This is advisable even if the assistant is fully trained.

These findings help to explain the discrepancies in the literature, referred to above. Laryngoscopy is the most basic of all anaesthetic techniques, but there seems wide variation in what is taught at different hospitals. Even at this hospital, which has above average awareness of the problem, there is clearly scope for improvement. Surprisingly, most textbooks do not describe the technique. Of course, it cannot be learnt from a book, but a brief text with drawings can be useful. Moreover, at least four of the texts which do describe laryngoscopy make no mention of cricoid pressure yet, in Wilson's study [8], cricoid pressure reduced the frequency of grade 3 from 9% to 1.5%. This might explain the high rates in the studies by Mallampati and colleagues [1] and Cohen, Laurito and Segil [9] (table V).

The true incidence of grade 3

Our interest in the frequency of grade 3 arose, in the first place, because of its crucial importance in emergency anaesthesia. Suboptimal laryngoscopy may not be important in routine surgery, because accidental oesophageal intubation should have no serious consequences in that context, but the emergency patient is different, as oesophageal intubation nullifies cricoid pressure and there may be regurgitation into the pharynx. The only way to guarantee tracheal intubation is to watch the tip of the introducer enter the trachea, which necessitates exposing the cords. Clearly, an anaesthetist who fails to see the cords only once in 292 patients [2] is in a better position than one to whom this happens once in eight patients [1].

Our original estimate [3] of grade 3 frequency was 1 in 2000—providing that care was taken to obtain the best possible view of the cords. This was, as stated, a "guesstimate" and may be too low but, equally, the surveys published (table V) are likely to give too high a frequency because of the factors discussed above.

One survey [2] seems to have obviated some of these reservations. One anaesthetist with a particular interest in obtaining an optimum view of the larynx, who kept a record of all intubations (3800) over a 7-yr period had an incidence of grade 3 of 1:292. There are several ways in which a false high incidence can arise, but it is not easy to see how a false low one can occur, so this, the lowest figure, is perhaps the best estimate.

Clinical relevance—training for obstetric anaesthesia

Our original study [3] was concerned mainly with training; from that standpoint, the precise incidence of grade 3 cases is not important because, even if the figure were as high as 3%, it is clear that many trainees would have little or no experience of difficult intubation by the time they begin to undertake emergency cases. This is particularly evident when the Poisson effect [10] is taken into account: if the average rate were 3%, then 5% of beginners $(e^{-3} \times 100)$ would see none in their first 100 intubations. It follows that a training method is needed which uses simulated difficult intubations. It seems worth stressing this point, because a recent editorial on obstetric anaesthesia [18] discussed antacid therapy at some length, but made no mention of difficult intubation. Similarly, other authorities have stated that there should be at least one consultant session per week in the maternity theatre for teaching purposes. A simple calculation shows that this teaching session would expect to see only about one difficult laryngoscopy per year, even in the busiest maternity unit, so clearly that suggestion does not solve the problem either.

Simulating difficult laryngoscopy is not justifiable in the maternity theatre; it has to be undertaken in the general theatres, on patients who are not at risk from regurgitation. The need for training of this type has been recognized by leading hospitals in the U.K.: the Royal United Hospital, Bath [8], the Royal Postgraduate Medical School [11] and the University Hospital, Cardiff [12]. The method is also on test in the U.S.A. [13, 14].

Possible hazards of the Macintosh method

Two possible hazards of the Macintosh method have been suggested: perforation of the pyriform fossa, and oesophageal intubation. Surveys [15–17] have shown the main cause of pyriform fossa perforation to be rigid stilettes. The Oxford tube was designed for use with a flexible introducer projecting from the end [Sir Robert Macintosh, personal communication], a point which has been re-emphasized [18]. Nearly 30 years ago, a survey of 18000 tracheal intubations with the Oxford tube [19] found no problems; our experience in the past 14 years supports this. Pyriform fossa perforation may occur even when no introducer is used, mainly in hasty emergency cases [20], but occasionally in routine cases [21]. The modern plastic tube is not so resilient as red rubber, so the risk of perforation is arguably higher during routine intubations than in the Macintosh method. Thus no ethical dilemma arises.

Accidental oesophageal intubation is more likely to occur with any blind method, but this should represent no risk to the patient. Most theatres are, or should be, equipped with carbon dioxide analysers; where these are not yet available the oesophageal detector device [22] is useful and inexpensive. Failure to diagnose oesophageal intubation, especially in the modern context, implies negligence. We conclude that informed consent is not needed for the simulated difficult intubation drill—a view supported by the Ethics Committee of this hospital.

Clinical relevance—making comparisons

As we have seen, the exact incidence of grade 3 cases is not important in relation to the need for training. However, it is important if the aim is to compare the frequency of difficult intubation in different situations. For example, it would be of value to know how often grade 3 cases occur in obstetrics compared with general surgery. Such studies would need to eliminate the sources of error noted above. It would help if each assessor acted as his own control, performing equal numbers of laryngoscopies in both fields. Such a trial could not be double-blind, which would be a serious weakness if the assessments were subjective—but, with the provisos noted above, laryngoscopy grading should be reasonably objective.

Clinical relevance—obstetrics

Two surveys [23, 24] have reported a failed intubation rate in obstetric anaesthesia of about 1 in 300. The second of these studies, by Samsoon and Young, also found that failed intubation was much more rare in general surgery (1 in 2200) than in obstetrics. Our prospective study, with no failures in 1387 cases, confirms their retrospective findings. Pooling the obstetric data [23, 24] gives 15 failed intubations in a total of 4380, which differs appreciably from 0 in 1387 ($P = 0.04$).

It has been suggested that pregnancy, by its effect on breast size, oedema of the pharyngeal tissues, etc., is the cause of the high failure rate. These changes certainly occur, but are they sufficient to make the difference between success and failure? At least one maternity unit has achieved results as good as those in general surgery. In the decade 1970–80, at the National Maternity and Mater Misericordiae Hospitals in Dublin, a total of 3800 general anaesthetics were given; there were only two failed intubations [J. McCarthy, personal communication]. Thus the Dublin maternity results are similar to those of Samsoon and Young for general surgery.

In the Dublin survey, all the anaesthetics were given by consultants and there seems no doubt that experience is a key factor. That was the main conclusion of our original study [3]. It has been suggested that a senior anaesthetist should be present for induction in all obstetric cases. This problem is analysed in more detail in a forthcoming review.

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British Journal of Anaesthesia 1991; **66**: 45–47

EFFECT OF ARTERIAL CARBON DIOXIDE TENSION ON THE DURATION OF ACTION OF ATRACURIUM

M. PLATT, A. HAYWARD, A. COOPER AND N. HIRSCH

SUMMARY

The duration of action of atracurium was studied in two groups of patients. In group I (n = 15), patients' lungs were hyperventilated to a mean Pa_{CO_2} *of 3.3 kPa and in group II (n = 15) lungs were ventilated to maintain a mean* Pa_{CO_2} *of 5.3 kPa. Anaesthesia was maintained using an infusion of propofol. The time taken to return to a T1 twitch height of 10% of control was measured following each incremental dose of atracurium 0.15 mg* kg^{-1}*. It was found that the duration of action of atracurium was significantly (P < 0.0005) shorter in the hypocapnic group.*

KEY WORDS

Biotransformation: atracurium. Carbon dioxide: arterial tension. Neuromuscular relaxants: atracurium

Atracurium is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action. This quaternary ammonium compound is unique in that its action is terminated by ester hydrolysis and Hofmann degradation [1–5]. The latter process is dependent on both pH and temperature [6]. Payne and Hughes [7] studied the effect of varying arterial carbon dioxide tensions on the rate constants for recovery from tetanic fade in five patients given atracurium, but their results were equivocal.

This study was designed to evaluate the effect of arterial carbon dioxide tension on the duration of action of incremental doses of atracurium in anaesthetized man.

PATIENTS AND METHODS

The study was approved by the National Hospital Ethics Committee and each patient gave verbal informed consent. We studied 30 patients undergoing various types of elective neurosurgery of 110–240 min duration, for which tracheal intubation and non-depolarizing neuromuscular block were required. All were ASA group I or II and aged 15–78 yr. Patients with renal, cardiovascular, hepatic or neuromuscular disorders were excluded. The patients were allocated randomly to one of two groups of 15 patients each: patients in group I underwent hyperventilation to a Pa_{CO_2} of 2.9–3.7 kPa (mean 3.3 kPa), while in group II a Pa_{CO_2} of 4.5–6.0 kPa (mean 5.3 kPa) was maintained.

No premedication was given. On arrival of the patient in the anaesthetic room, surface electrodes were placed over the ulnar nerve at the wrist and the ipsilateral hypothenar eminence, so that evoked electromyograph recordings could be made using a Datex Relaxograph as described by Carter and colleagues [8]. Anaesthesia was induced with fentanyl 1.5 $\mu g\ kg^{-1}$ and propofol 1–2 mg kg^{-1}, followed immediately by an infusion of propofol for maintenance of anaesthesia [9]. The infusion was started at a rate of 12 mg $kg^{-1}\ h^{-1}$, and reduced as described elsewhere [9] to a maintenance rate of 6–8 mg $kg^{-1}\ h^{-1}$, according to the needs of the patient.

The lungs were ventilated artificially with 50% nitrous oxide in oxygen. No volatile anaesthetic agents were used. Following calibration of the Relaxograph, atracurium 0.6 mg kg^{-1} was given to facilitate tracheal intubation. A Cape Waine ventilator was used with a semiclosed breathing system incorporating a soda-lime cannister. Hyperventilation was produced by increasing tidal volume up to 14 ml/kg body weight. Ventilation frequency was adjusted to 12–15 b.p.m. to obtain

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the desired hypocapnia. Both tidal volume and frequency were reduced for normocapnia.

ECG, intra-arterial pressure (from a cannula inserted into a radial artery), end-tidal carbon dioxide concentration (Cardiocap infra-red analyser) and nasopharyngeal temperature were recorded throughout the procedure. Temperature was maintained at 36.3 ± 0.6 °C, using a warming blanket, a condenser humidifier and blood warmer. Arterial blood-gas tensions were measured at the following times: in the anaesthetic room and during the procedure, following the induction dose of atracurium, and following each incremental dose of atracurium.

When the first twitch (T1) amplitude reached 10% of the baseline value, a bolus of atracurium 0.15 mg kg^{-1} was given. On each occasion that T1 returned to 10%, a further increment was given. The time between each incremental dose was recorded.

Data were analysed statistically using an unpaired *t* test and regression analysis. To avoid bias caused by the variation in the number of observations for each patient, a grand mean incremental time was obtained for each group, and the mean incremental time and Pa_{CO_2} for each patient were used in the data analysis.

RESULTS

There were no significant differences between the two groups for age and weight (table I). The mean Pa_{CO_2} was 3.3 (SD 0.28) kPa in group I and 5.3 (0.32) kPa in group II ($P < 0.001$). Mean pH was 7.50 (0.04) in group I and 7.34 (0.05) in group II ($P < 0.001$) (table II).

The mean duration of action of atracurium in group I was 17.9 (3.2) min and that in group II was 22.8 (3.1) min ($P < 0.0005$) (table III (grand means), fig. 1 (mean incremental time for each patient)).

TABLE I. *Comparison of age and weight between groups I and II (mean* (SD) *[range])*

	Group I (n = 15)	Group II (n = 15)
Age (yr)	49.9 (19.4) [15.0–71.0]	55.3 (16.2) [24.0–78.0]
Weight (kg)	77.8 (12.19) [55.0–97.8]	68.5 (13.58) [50.0–95.0]

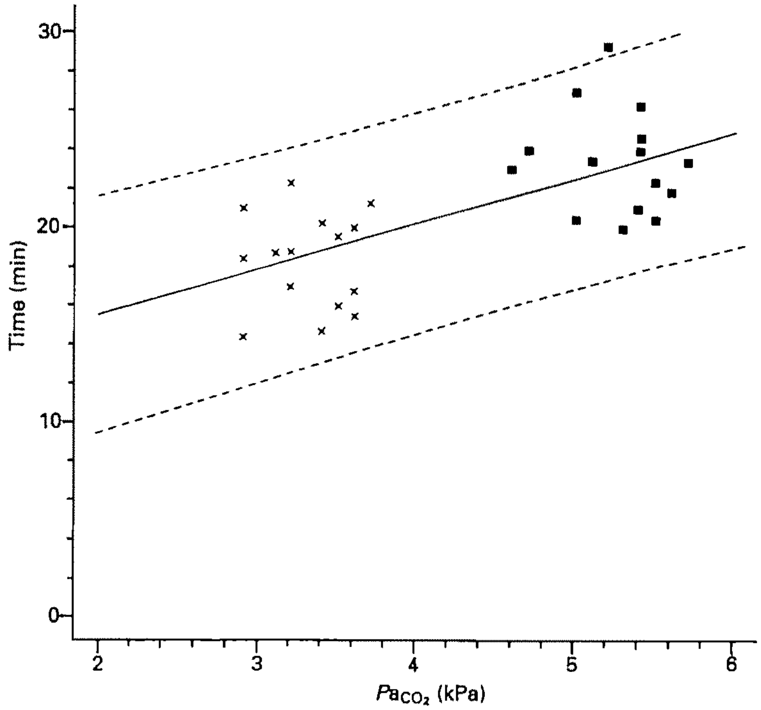

FIG. 1. Plot of mean duration of action of atracurium in each patient against Pa_{CO_2}. Solid line = regression line $y = 10.80 + 2.36x$ ($r = 0.67$); dotted lines = 95% confidence limits. x = Hypocapnic group; ■ = normocapnic group ($P < 0.0005$).

TABLE II. *Comparison of arterial* Pa_{CO_2} *and pH in groups I and II (mean* (SD) *[range])*

	Group I ($n = 15$)	Group II ($n = 15$)	*P*
Pa_{CO_2} (kPa)	3.3 (0.28) [2.9–3.7]	5.3 (0.32) [4.6–5.7]	< 0.001
pH	7.50 (0.04) [7.45–7.57]	7.35 (0.05) [7.24–7.43]	< 0.001

TABLE III. *Comparison of duration of action of incremental doses of atracurium (mean* (SD) *[range])*

	Group I	Group II	*P*
No. observations	85	53	
Duration (min)	17.9 (3.2) [11.0–27.0]	22.8 (3.1) [16.0–30.0]	0.0005

DISCUSSION

Although the duration of action of most non-depolarizing neuromuscular blocking agents is influenced by temperature and pH [10], atracurium has a duration of action which is more dependent on these factors. *In vitro* studies [11] have shown that Hofmann degradation of atracurium is at least three times as rapid when the pH is increased from 6.9 to 7.6. Studies on cats have demonstrated that the duration of action of atracurium is reduced significantly when arterial pH is increased from 7.31 to 7.63 by hyperventilation [3, 11].

Payne and Hughes [6] demonstrated that recovery from neuromuscular block after atracurium was faster during hyperventilation in three of the five patients studied. In one patient recovery was unchanged, while in the remaining patient recovery was slower during hyperventilation. Each patient acted as their own control; an increase in pH in the range 0.16–0.28 kPa was achieved.

Fisher and colleagues [12], devised a model suggesting that 39% of the clearance of atracurium is produced by Hofmann elimination and ester hydrolysis, indicating a large fraction of atracurium clearance is pH-dependent.

In this study, we have confirmed that respiratory alkalosis shortens significantly the duration of action of atracurium in anaesthetized man, as expected from the large fraction of atracurium which is cleared by pH-dependent means.

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British Journal of Anaesthesia 1991; **66**: 48–52

INGESTION OF CLEAR FLUIDS IS SAFE FOR ADOLESCENTS UP TO 3 H BEFORE ANAESTHESIA

W. M. SPLINTER AND J. D. SCHAEFER

SUMMARY

We have studied the effect of ingestion of unlimited clear fluids by adolescents up to 3 h before anaesthesia to determine the effect this fluid ingestion would have on thirst, hunger and gastric contents at induction of anaesthesia. We studied prospectively 152 adolescents (ages 13–19 yr) undergoing elective surgery. Fifty percent of the patients had nothing by mouth after midnight. The other 50% were instructed to ingest unlimited clear fluids up to 3 h before surgery. On arrival in the operating room, subjects were asked to assess thirst and hunger with a linear analogue scale of 0–10 (0 corresponding to no thirst or no hunger). After induction of anaesthesia, gastric contents were aspirated via a 16-French gauge orogastric tube. Gastric fluid volume (GV) was measured with a syringe and gastric pH (GpH) was assessed with Merck pH strips. GV, GpH and subject hunger were unaffected by ingestion of clear fluids. Subject thirst was reduced by clear fluids. It is concluded that unlimited clear fluid ingestion by healthy adolescents up to 3 h before operation decreases thirst and does not affect gastric contents.

KEY WORDS

Anaesthesia · general. Gastrointestinal tract · gastric fluid volume, gastric pH, preoperative fluids.

The ingestion of clear fluids by patients on the day of surgery is being reviewed [1–8]. There is no physiological evidence to support the guidelines suggesting 4–6 h abstention from clear fluids by healthy patients before elective surgery. It has been shown that healthy adults may ingest limited volumes (only 150 ml) of clear fluids up to 2–3 h before anaesthesia [7, 8]. For adolescents, there is no evidence for or against the view that abstention from clear fluid is necessary on the day of surgery. Also, it has not been established if preoperative ingestion of clear fluids would benefit adolescents.

This study was designed to determine if adolescents could ingest unlimited volumes of clear fluids up to 3 h before surgery without affecting gastric contents, and to determine if this would decrease patient thirst and hunger. Also, we wished to examine if the gastric content of adolescents was influenced by gender, age, weight and inpatient/outpatient status.

PATIENTS AND METHODS

With Hospital Ethics Committee approval and with parental or patient informed consent, we studied 152 healthy adolescents, aged 13–19 yr, ASA physical status I or II allocated randomly to one of two groups. Patients were excluded if there was a history of gastrointestinal disease, if surgery was non-elective, or if their medication affected gastric contents.

It had been our usual practice to ask patients to fast after midnight of the evening before surgery. Fifty percent of the subjects (76) followed this standard procedure. The other 50% were instructed to have unlimited clear fluids until 3 h before operation. Clear fluids were defined as clear aqueous solutions which were liquid at 37 °C. Typical fluids ingested included apple juice, water, jelly (Jello in North America) and lemonade (soda pop in North America). Immediately before surgery, the patients completed

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TABLE I. *Patient data (mean (SD))*

Group	n	Age (yr)	Weight (kg)	Percent inpatients	Volume ingested (ml)	Fast (h)
Overnight fast	76	15 (2)	60 (16)	36	0	12.7 (2.5)
3-h fast	76	15 (2)	56 (11)	49	270 (190)	3.6 (0.8)

a questionnaire (LAS) on hunger and thirst using a 10-cm linear analogue scale on which 0 corresponded to no thirst or no hunger and 10 represented severe hunger and thirst.

Anaesthesia was induced by whatever technique the consultant anaesthetist deemed most appropriate. The trachea was intubated when indicated. After establishment of adequate anaesthesia, a 16-French gauge orogastric tube was passed into the stomach by an investigator who was unaware of the subject's fasting status. The position of the orogastric tube was confirmed by auscultation. Stomach contents were aspirated with the gastric tube in several positions and the patient tilted to the right, left, head-down and head-up positions. Gastric fluid volume (GV) was measured with a 20-ml syringe and gastric pH (GpH) was measured with pH paper (Merck pH 0–14 and pH 0–2.5). Gastric volumes of less than 1 ml were approximated to a value of 0.5 ml.

For the purpose of this investigation patients considered to be "at risk" of aspiration pneumonia had either GV > 1.0 ml kg^{-1} or the combination of GV > 0.4 ml kg^{-1} and GpH < 2.5 [9–11].

Normally distributed data were analysed using Student's *t* test, non-parametric data were analysed with Mann–Whitney *U* test, chi-square test and Fisher's exact test. Relationships between GV or GpH and gender, age, weight and length of

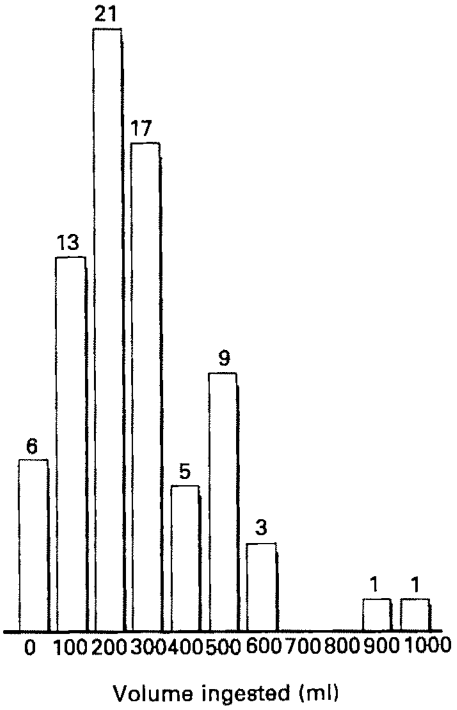

FIG. 1. Volumes of clear fluid ingested on the day of surgery (values represent midpoint of grouping). The number of patients in each grouping is given (total $n = 76$).

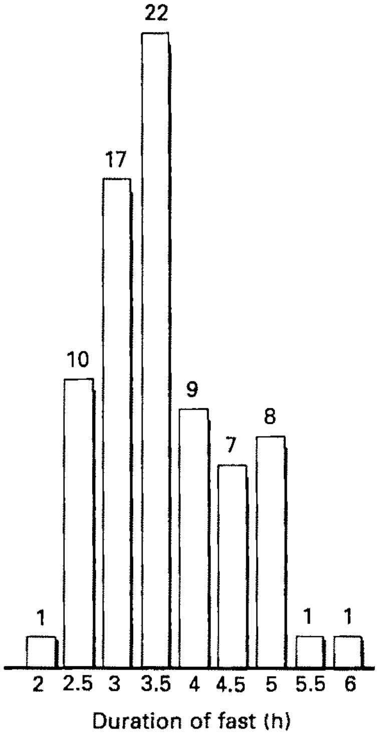

FIG 2 Duration of clear fluid fast (values represent midpoint of grouping) The number of patients in each grouping is given (total $n = 76$).

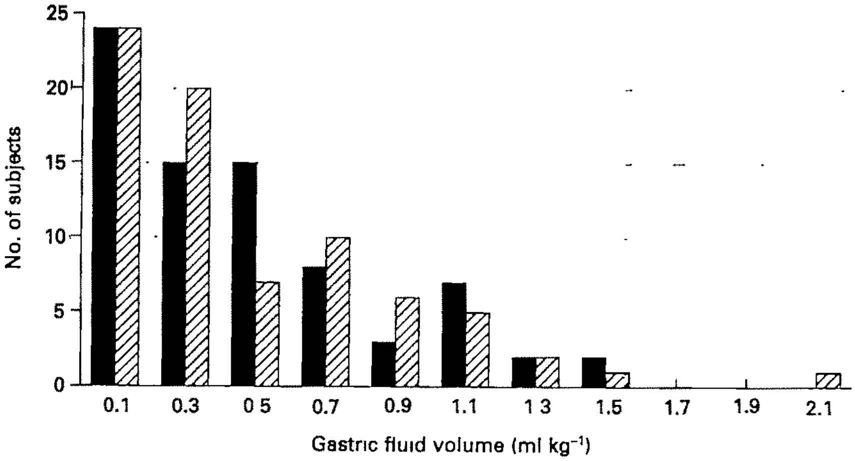

FIG. 3. Distribution of gastric fluid volume among the subjects (values represent midpoints of groupings). ■ = 3-h fast; ▨ = overnight fast.

fast were analysed using linear regression analysis. Values were considered to be significantly different if $P < 0.05$. Sample size was determined to test for equivalence of interventions; alpha was set at 0.05 and beta set at 0.10.

RESULTS

The groups were similar with respect to age, weight, gender, ASA physical status, and inpatient/outpatient status (table I). Adolescents who were allowed clear fluids ingested 10–1000 ml (mean 270 (SD 190) ml) on the day of surgery (fig. 1). The clear fluid fast was of 2.2–6.0 h (3.6 (0.8) h) among the adolescents permitted fluids on the day of their operation (fig. 2).

Gastric fluid volumes and gastric pH were similar in the two groups (table II, figs 3, 4). Gastric fluid volume and gastric pH of the 28 patients who ingested clear fluid 3 h or less before anaesthesia was similar to that of those who abstained from food and drink on the day of surgery; this subgroup had a gastric fluid volume of 0.40 (range 0.02–1.13) ml kg^{-1} and a gastric pH of 1.7 (1.3–4.0).

TABLE II. *Volume of gastric contents (mean (SD) [range])*

Group	Volume (ml kg^{-1})	pH
Overnight fast	0.48 (0.40) [0.02–2.11]	1.6 (0.4) [1.2–3.0]
3-h fast	0.46 (0.39) [0.02–1.47]	1.8 (1.0) [1.2–6.5]

Adolescents who ingested clear fluids on the day of surgery did not have an increased incidence of "at risk" gastric contents (table III).

Gastric fluid volume and pH were unaffected by patient age, weight, gender, inpatient/outpatient status, duration of fast and volume ingested. Inpatients ingested more clear fluids than outpatients ($P < 0.02$, 95 % confidence limits 22–187 ml).

The adolescents permitted clear fluid had decreased thirst on the day of surgery. Patient hunger at the time of surgery was unaffected by ingestion of clear fluid (table IV).

DISCUSSION

The ingestion of unlimited volumes of clear fluids by healthy adolescents up to 3 h before elective

TABLE III. *Number of patients with large volume gastric contents*

Group	*n*	Volume > 0.4 ml kg^{-1} and pH < 2.5	Volume > 1.0 ml kg^{-1}
Overnight fast	76	36	9
3-h fast	76	38	11

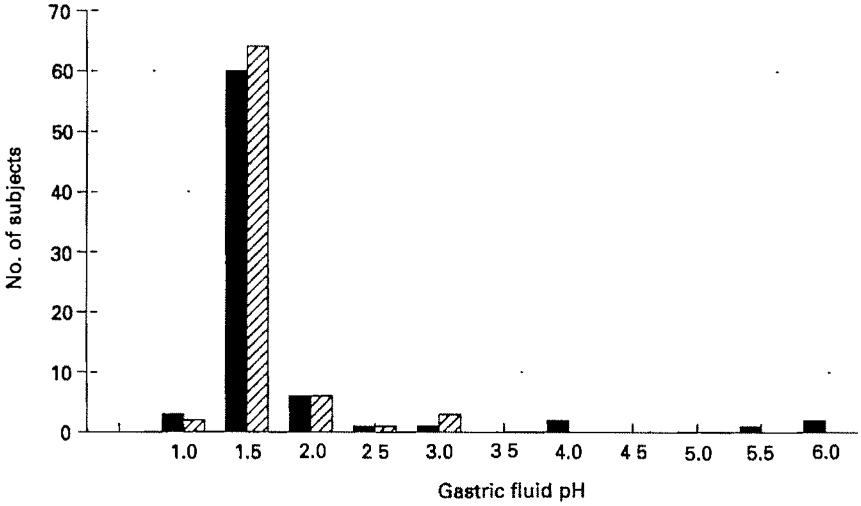

FIG. 4. Distribution of gastric pH among the subjects (values represent midpoints of groupings). ■ = 3-h fast; ▨ = overnight fast.

surgery decreased thirst and did not affect gastric fluid volume and pH measured at the onset of anaesthesia. Gastric volumes and pH were similar to those observed in adults and children [1–8].

The methods used to measure gastric contents are not exact. Gastric aspiration underestimates gastric fluid volume, but it correlates well with true GV [12], removing 60–90% of gastric fluid volume. Each patient's GV was measured in a similar fashion, thus any underestimation would be observed in both groups. On the other hand gastric pH may be measured accurately with Merck pH sticks [13, 14].

No patient variable studied (age, weight, gender, inpatient/outpatient status) was found to affect gastric contents. Subject age has been shown to affect gastric volume and pH, but this was not observed over the narrow age range of this study [15]. Ong [16] observed larger residual gastric volumes among adult outpatients. Outpatient/inpatient status does not appear to affect adolescents' gastric fluid volume. Further study is required to determine if outpatients have increased gastric volumes.

TABLE IV. *Patient thirst and hunger (median (range)). *P < 0.05, Mann–Whitney* U *test*

Group	Thirst	Hunger
Overnight fast	4.0 (0–10)	6.0 (0–10)
3-h fast	5.0 (0–10)*	5.5 (0–10)

The subjects in this study ingested variable amounts of clear fluids. This may reflect the variable eating habits typically observed in adolescents. A few teenagers may have ingested less than normal because of their awareness of past fasting guidelines. Inpatients ingested more fluid than outpatients, possibly because of greater availability of clear fluids; for example, they were offered a clear fluid breakfast.

Ingestion of clear fluids decreased thirst, but had no effect on hunger. Several subjects told us their hunger increased after ingesting fluids.

Clear fluids, such as water, clear fruit juices and jelly, rapidly empty from the stomach because gastric emptying of clear fluids follow first-order kinetics. The ingestion of solid food and non-clear fluids on the day of surgery is not recommended, as they empty according to zero-order kinetics.

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PHARMACOKINETICS AND CLINICAL EXPERIENCE OF 20-H INFUSIONS OF METHOHEXITONE IN INTENSIVE CARE PATIENTS WITH POSTOPERATIVE PYREXIA

F. REDKE, S. BJÖRKMAN AND B. ROSBERG

SUMMARY

We have studied the pharmacokinetics of 20-h infusions of methohexitone in young patients with postoperative fever undergoing artificial ventilation of the lungs. The infusion rate was adjusted so that patients were unresponsive to vocal stimulation but reacted to tracheal suction. The mean steady state concentration of methohexitone required was 2.6 mg litre^{-1} (unbound 0.53 mg litre^{-1}). The mean (SD) total clearance of methohexitone was 16.3 (4.2) ml min^{-1} kg^{-1}, which is greater than that for volunteers or normal surgical patients. The unbound clearance correlated positively with body temperature during the infusion ($r = 0.796$, $P = 0.017$). The terminal half-life of methohexitone was 6.3 (3.8) h and that of the 4′-hydroxy metabolite 5.8 (2.1) h. There were no marked haemodynamic effects of the infusion, and no excessive sedation after the infusion. However, the clearance of methohexitone was high and variable, possibly as a direct effect of postoperative fever. Consequently, the need for individual titration of the rate of infusion is emphasized.

KEY WORDS
Anaesthetics, intravenous methohexitone. Pharmacokinetics.

The use of long-term or high-dose infusions of methohexitone for sedation or total i.v. anaesthesia is controversial. Undesirable haemodynamic effects [1, 2], excessive post-infusion sedation [3] and convulsions [2] have been reported following such infusions.

The pharmacokinetics of methohexitone in adults has been investigated after i.v. bolus in surgical patients [4, 5] and volunteers [5] and with short-term infusions in volunteers [6]; fairly consistent results have been obtained. However, studies with hexobarbitone [7] suggest that pharmacokinetic data from volunteers or "normal" surgical patients may not apply to intensive care patients, in whom physiological functions are altered by factors such as trauma, infection, fever and multi-drug treatment. Thus the clearance of methohexitone was found to be substantially greater in patients with hepatitis than in normal subjects [8]. During and after long-term (14 h) infusions in elderly patients recovering from major surgery, the clearance of methohexitone was comparable to that in volunteers and surgical patients, while the volume of distribution was increased markedly and the terminal half-life prolonged [3].

The objectives of this investigation were to evaluate the pharmacokinetics and clinical performance of methohexitone in long-term infusions in young intensive care patients with postoperative fever.

PATIENTS AND METHODS

Design of study

The study was approved by the Ethics Committee of the University of Lund. Informed consent was obtained from 10 young patients (six male) aged 20–41 yr with normal heart, lung, kidney and liver function. All patients were undergoing surgery of the jaw and were operated on by the same surgeon. No patient was receiving any medication before surgery. Haemoglobin,

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thrombocyte, leucocyte, liver enzyme and serum electrolyte concentrations were measured before and after operation. Patients were premedicated with pethidine 0.8–1.3 mg kg^{-1}, dixyrazine (a major tranquillizer) 0.2–0.5 mg kg^{-1} and atropine 0.5 mg. General anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and maintained with enflurane and 70% nitrous oxide in oxygen ($F\text{I}_{\text{O}_2}$ 0.3) supplemented with fentanyl 0.01–0.02 mg kg^{-1}. Suxamethonium 1.3–2.8 mg kg^{-1} was used to facilitate tracheal intubation.

Before recovery, the patients were transferred from the operating theatre to the intensive care unit (ICU), where the lungs were ventilated artificially with air and oxygen ($F\text{I}_{\text{O}_2}$ 0.3). Arterial Pa_{O_2} was maintained at 15–18 kPa and Pa_{CO_2} at 4.6–5.6 kPa. An infusion of methohexitone for sedation was started just after the patient's arrival in the ICU. Systemic arterial pressure was measured continuously via a radial artery cannula. Body temperature was measured by a rectal probe and recorded every 1 h. Venous blood samples were taken before and 4, 8, 12, 16 and 20 h after the start of the infusion and 0.5, 1, 2, 4, 8, 12, 16 and (if feasible) 24 h after the infusion was stopped. A solution of methohexitone sodium (Brietal) 2 g in 5% glucose 500 ml was delivered by a volume controlled IVAC infusion pump. The clinical status of the patient was evaluated at least every 1 h by a nurse who was in continuous attendance. The infusion rate was adjusted to provide sedation that allowed the patient to be unresponsive to vocal stimulation but react to tracheal suction, which was performed as needed. All changes in infusion rate were noted. The sedation was supplemented with analgesics (pethidine, phenoperidine or piritramide) when the patient was in pain. The total doses given were: pethidine 0.4–1.8 mg kg^{-1} (four patients), phenoperidine 0.02–0.22 mg kg^{-1} (eight patients) and piritramide 0.13–0.28 mg kg^{-1} (two patients). Paracetamol was used to decrease body temperature if it exceeded 39.5 °C. A neuroleptic drug (dixyrazine 0.7 mg kg^{-1} or droperidol 0.04–0.07 mg kg^{-1}) was administered if further sedation was needed and the systolic arterial pressure was 100 mm Hg or less. All patients were given cefuroxime 4.5 g i.v. in divided doses during the infusion.

Assay of methohexitone

The blood samples were centrifuged and plasma stored at −20 °C until assay. Methohexitone and its 4′-hydroxy metabolite concentrations were measured by gas–liquid chromatography with nitrogen-selective detection, after slight modifications to the original procedure [9]. Briefly, 0.2–1.0 ml samples of plasma were adjusted to pH 6.5 with Na_2HPO_4 solution and extracted with cyclohexane:dichloromethane (1:1) 4 ml after addition of hexobarbitone 2 µg as internal standard. After evaporation of the solvents, the extracts were injected onto a gas chromatograph with an OV-17 packed column as described [9]. The coefficient of variation of the assay was around 4% over the range 0.13–2 µg per sample. The metabolite was identified by its chromatographic retention time relative to those of methohexitone and hexobarbitone [9], and by its presence only in plasma and urine samples from patients treated with methohexitone. As we did not have access to pure metabolite, it could not be assayed in absolute concentrations; however, its terminal half-life could be calculated from concentrations expressed in arbitrary units (peak height of metabolite *vs* that of the internal standard).

The unbound fraction (*F*u) of methohexitone and the metabolite were measured using a Centrifree Micropartition System (Amicon, U.S.A.), as described previously [10].

Pharmacokinetic calculations

A model-independent approach was used for calculation of clearance and volume of distribution of methohexitone.

The area under the plasma concentration curve (AUC) and the area under the first moment curve (AUMC) were calculated by the logarithmic trapezoid method [11]. Total body clearance (Cl^{area}) was calculated as dose/AUC. The unbound clearance (Clu^{area}) was calculated as $Cl^{\text{area}}/F\text{u}$. The volume of distribution at steady state (V^{ss}) was calculated as:

$$V^{\text{ss}} = \frac{\text{Dose}\cdot\text{AUMC}}{(\text{AUC})^2} - \frac{t\cdot\text{Dose}}{2\cdot\text{AUC}}$$

where t is the duration of the infusion (20 h) (cf [11]).

The terminal half-lives of methohexitone and the metabolite were determined by curve-stripping of the post-infusion concentration data followed by weighted non-linear regression. Redistribution half-lives were not characterized. Weighting of the data points was by concen-

TABLE I. *Individual characteristics of the patients, anaesthesia and methohexitone infusions. The total dose is given as the methohexitone free acid.* † *Mean* (SD)

Patient No.	Sex	Weight (kg)	Age (yr)	Cigarette smoker?	General anaesthesia (min)	End anaesthesia to start methohexitone (min)	End methohexitone to extubation (min)	Methohexitone final infusion rate (mg kg^{-1} h^{-1})	Total dose infused (g)	†Body temp. during infusion (°C)
1	M	80	20	No	180	35	45	3 22	4.56	38.7 (0.62)
2	M	95	20	Yes	195	40	40	2.71	5.01	38.8 (0.59)
3	M	72	27	No	205	30	45	3.58	4.74	39.1 (0.61)
4	F	63	20	Yes	135	40	25	3.50	4.68	38.7 (0.62)
5	M	60	22	No	205	45	60	3.68	4.34	38.4 (1.08)
6	M	58	25	No	260	30	80	4.48	4.39	38.1 (0.58)
7	F	79	41	No	235	25	20	1.63	2.37	38.0 (0.91)
8	M	74	26	Yes	230	60	65	3.23	4.45	38.6 (0.83)
9	F	53	26	Yes	185	30	30	4.56	4.62	38 5 (1.00)
10	F	54	22	Yes	145	25	70	4.77	3.93	37.9 (0.91)
Mean		69	25		198	36	48	3.54	4 31	
SD		14	6.3		39	11	20	0.94	0.74	

tration^{-1}. The RSTRIP software (Micro Math Inc., U.S.A.) was used, giving half-lives as mean (SD).

RESULTS

Data on individual patients, anaesthesia and infusion rates of methohexitone needed to maintain the pre-determined degree of sedation are shown in table I, which also shows mean body temperatures during the infusion. The initial step-wise dose titration took between 1 and 8 h (median 4.5 h). It was then possible to maintain a reasonably constant infusion rate in most patients.

The plasma concentration curves of methohexitone are shown in figure 1 and the pharmacokinetic parameters of methohexitone in the 10 patients in table II. The total plasma concentration needed for adequate sedation varied between 1.5 and 8.6 mg litre^{-1} (mean (SD) 2.6 (1.1) mg litre^{-1}). The corresponding range for unbound concentration was 0.35–1.89 mg litre^{-1}, (mean 0.53 (0.18) mg litre^{-1}). The mean total plasma concentration at the end of infusion was 4.1 (2.0) mg litre^{-1} (unbound 0.80 (0.33) mg litre^{-1}).

In patient No. 3, Cl^{area}, Clu^{area}, total and unbound concentrations needed for sedation, in addition to total and unbound concentrations of methohexitone at the end of infusion, deviated by 2.33–7.43 SD from the mean values cited above and in table II. V^{ss} deviated by 2.08 SD. These data were therefore not included in the calculations of mean values.

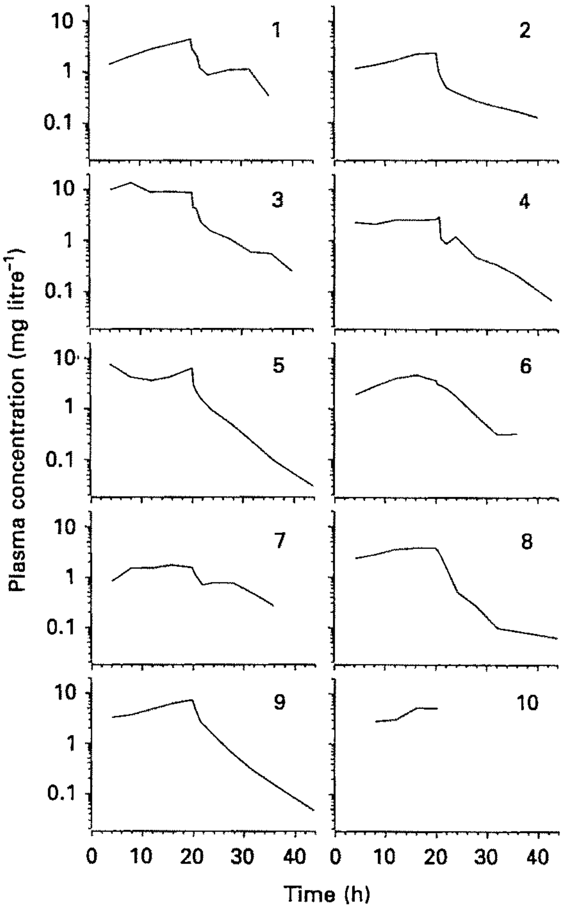

FIG. 1. Plasma concentration curves of methohexitone in individual patients.

TABLE II. *Pharmacokinetic parameters of methohexitone (M) and the 4′-hydroxy metabolite (Met).* $AUC = AUC_{0\text{-}4h}$ *[extrapolated residual area];* Cl^{area} *= total body clearance of M, calculated from* $AUC_{0\text{-}\infty}$*, where possible;* Clu^{area} *= unbound clearance;* $T_{\frac{1}{2}}$ *= fitted terminal half-life (mean (SD));* V^{ss} *= apparent volume of distribution at steady-state; Fu = unbound fraction in plasma (mean of two determinations)*

Patient No.	AUC (mg h^{-1} litre^{-1})	Cl^{area} (ml min^{-1} kg^{-1})	Clu^{area} (ml min^{-1} kg^{-1})	$T_{\frac{1}{2}}M$ (h)	$T_{\frac{1}{2}}Met$ (h)	V^{ss} (litre kg^{-1})	Fu_M (%)	Fu_{Met} (%)
1	65.6 [—]	14.5	81	—	7.9 (2.44)	5.68	18	59
2	36.2 [1.8]	23.1	105	9.3 (1.04)	5.2 (0.23)	9.55	22	64
3	205.9 [2.0]	[5.3]	[24]	5.5 (0.62)	7.8 (0.55)	[0.87]	22	66
4	55.2 [0.4]	22.2	106	4.4 (1.21)	7.5 (2.17)	6.58	21	68
5	105.6 [0.2]	11.4	57	4.0 (0.24)	3.8 (0.48)	1.62	20	66
6	74.9 [1.6]	16.5	69	3.7 (0.25)	5.8 (1.51)	5.65	24	64
7	35.0 [—]	14.3	57	—	—	5.39	25	65
8	66.7 [1.2]	14.7	78	13.6 (13.9)	2.1 (0.41)	5.87	19	60
9	106.2 [0.2]	13.7	76	3.7 (0.40)	6.2 (0.65)	3.98	18	65
10	—	—	—	—	—	—	19	68
Mean		16.3	79	6.3	5.8	5.54	21	65
SD		4.17	18.8	3.77	2.05	2.24	2.4	3.0

Comparison of the half-life of the metabolite with that of methohexitone was complicated by the fact that the decay curves of methohexitone were markedly poly-exponential, while those of the metabolite were mainly mono-exponential. This was especially true for patient No. 8, in whom a late, long half-life could be defined for methohexitone but not for the metabolite. However, the turnover of the metabolite is apparently formation rate limited.

In two patients (Nos 1 and 7) the decline in plasma concentration of methohexitone was not smooth, and no terminal half-life could be defined. In patient No. 4 there was a minor secondary plasma concentration peak.

Figure 2 shows two primary pharmacokinetic parameters in individual patients plotted against the mean body temperature during the infusion. Smokers had a significantly greater unbound clearance of methohexitone than non-smokers (91 (16.5) *vs* 66 (11.5) ml min^{-1} kg^{-1}; $P < 0.05$, two-tailed *t* test, patient No. 3 excluded).

Recovery from sedation was smooth in all patients. Artificial ventilation was discontinued 48 (20) min after the infusion (table I), and patients were fully awake (orientated in time and space and able to give name and date of birth) within 1.5 h.

All patients had varying degrees of postoperative pyrexia (table I, fig. 2). Moderate tachycardia and increased pulse pressure caused by the pyrexia complicated assessment of the haemodynamic effects of the methohexitone infusion. As is apparent from table III, the infusion had marginal, if any, effect on mean arterial pressure.

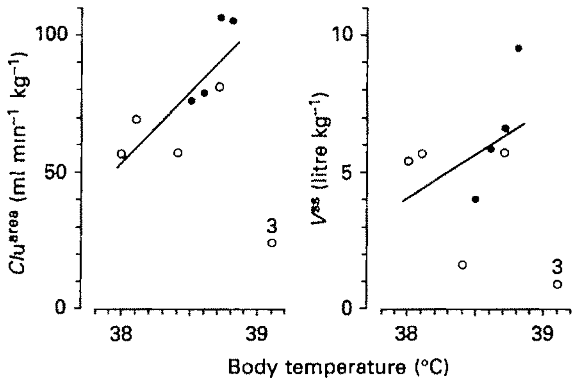

FIG. 2 Unbound clearance (Clu^{area}) and volume of distribution at steady state (V^{ss}) plotted against mean body temperature during the infusion. ● = Smokers; ○ = non-smokers The regression of Clu^{area} *vs* temperature is significant ($P = 0.017$, $r = 0.796$), temperature accounting for 63% of the variance in Clu^{area} (When the total clearance, Cl^{area}, was plotted against temperature, the regression just failed to achieve significance: $P = 0.086$, $r = 0.602$.) The line drawn through the V^{ss} data points would be the line of "best fit", but the regression is not significant ($P = 0.307$, $r = 0.415$). Data from patient No. 3 were excluded from all calculations.

Patients Nos 1–9 showed no evidence of liver impairment during or after the infusion of methohexitone. Circulating aspartate aminotransferase (AST) and bilirubin remained within normal values and showed no tendency to increase. However, in patient No. 10, exposed

TABLE III. *Haemodynamic changes during the study (mean (SD)) (n = 10). *P < 0.05 compared with previous value*

Period	MAP (mm Hg)	Heart rate (beat min^{-1})
Before anaesthesia	88 (7.9)	73 (10.8)
During anaesthesia	89 (9.8)	71 (7.3)
Between anaesthesia and start of infusion	97 (12.1)	71 (14.9)
During infusion	96 (8.5)	88 (12.4)*
After recovery	97 (12.0)	89 (10.4)

previously to halothane anaesthesia in her childhood, some pallor and a 28-mm Hg reduction in mean arterial pressure were observed at the end of the infusion; liver enzymes increased to maximum values of: AST 8580 u litre^{-1} (normal < 35 u litre^{-1}); alanine aminotransferase 11420 u litre^{-1} (normal < 35 u litre^{-1}); lactate dehydrogenase 7400 u litre^{-1} (normal < 500 u litre^{-1}). Serum bilirubin was 130 μmol litre^{-1} (normal < 20 μmol litre^{-1}) 4 days after the end of the infusion. All liver function values returned to normal within 3 weeks. Tests for viral hepatitis were negative.

DISCUSSION

The total plasma concentration of methohexitone needed to maintain deep sedation (1.5–8.6, mean 2.6 mg litre^{-1}) is slightly less than the therapeutic window for hypnotic effects (3.4–10.7 mg litre^{-1}) reported by Lauven, Schwilden and Stoeckel [12]. Sporadic administration of opioid analgesics may have led to a decreased demand for methohexitone in our patients compared with that of unpremedicated volunteers in Lauven's study. The plasma concentrations in our patients can be compared also with reported target methohexitone concentrations for i.v. anaesthesia, in conjunction with 67% nitrous oxide in oxygen, of 10 mg litre^{-1} [13] or 5 mg litre^{-1} [14].

The mean clearance of methohexitone in our patients (16.3 ml min^{-1} kg^{-1}) was greater than in young volunteers (12.1 ml min^{-1} kg^{-1}) [6], surgical patients (10.9 ml min^{-1} kg^{-1}) [4]; 8.2–9.3 ml min^{-1} kg^{-1} [5]) or in elderly postoperative patients (9.3–9.8 ml min^{-1} kg^{-1}) [3]. This increase in clearance may be a result of several factors, for example fever, changes in liver blood flow or induction of hepatic mixed function oxidases.

Induction of hepatic enzymes in conjunction with increased liver blood flow in intensive care patients may increase the clearance of methohexitone to 35 (17) ml min^{-1} kg^{-1} [8]. Also, the hepatic clearance of hexobarbitone could be enhanced considerably in intensive care patients, in particular in those with infection and fever [7]. Pyrexia may increase the rate of elimination of drugs [7, 15]. However, to our knowledge, conclusive evidence for this has been presented for two drugs only, phenytoin [16] and melphalan [17]. Pyrexia caused by upper respiratory tract infections in children increased the hepatic clearance of phenytoin, while that of phenobarbitone was unchanged. Because of its non-linear elimination kinetics, the clearance of phenytoin is very sensitive to changes in hepatic enzyme activity [16]. Melphalan is eliminated to a large extent by non-enzymic chemical cleavage [17]. Pyrogen-induced fever was shown [18] to increase total liver blood flow markedly in man, both in absolute values and as a percentage of cardiac output. In our patients, the unbound clearance of methohexitone correlated positively with body temperature. The hepatic extraction ratio (*E*) of methohexitone under "normal" conditions has been estimated to be 0.5 [4] or 0.7 [8]. This implies that clearance of methohexitone is moderately sensitive to changes in hepatic blood flow, and that increased liver blood flow during fever may increase the clearance.

Data from patient No. 3 were excluded from the calculations. The patient was of Philippine origin (the other patients were Caucasians) and had viral hepatitis several years previously. The connection between this and the aberrant pharmacokinetics and -dynamics of methohexitone is not clear. It should be noted, however, that this patient had the highest temperature.

Fevers of different aetiology are mediated through a common biochemical pathway, production of interleukin-1, thus causing similar physiological and biochemical changes [19]. Therefore, it is likely that fevers of different origin may have a similar influence on pharmacokinetics.

It is possible that induction of hepatic mixed function oxidases occurred during the 20-h infusions. Enzyme induction by barbiturates is generally thought to take several days, but adequate studies of the time-course and dose-dependency in humans are lacking. There is some evidence that a single large dose of barbiturate can cause substantial auto-induction of metabolizing enzymes [20]. There was no apparent enzyme induction in the patients treated by Le Normand and colleagues [3]; however, the methohexitone infusion was 6 h shorter than in our study, and in elderly patients the capacity for enzyme induction may be low, as has been shown with antipyrine [21]. In our young patients, enzyme induction might have occurred. It should be noted also that the cigarette smokers showed a significantly greater clearance of methohexitone than the non-smokers, presumably because of prolonged induction of liver enzymes.

There is no obvious reason to suspect that concomitant medication during the study period could have affected the disposition of methohexitone. Cefuroxime, the only other drug given in large doses to all patients, is excreted renally and not metabolized by the liver [22]. The opioid and neuroleptic drugs given during the infusion could not have influenced the disposition of an approximately 100-fold greater molar dose of methohexitone.

No attempt was made to follow the plasma concentration of methohexitone during the initial dose titration phase. The AUC was calculated on the assumption that the plasma concentration increased linearly with time until the first blood sampling at 4 h. With a constant rate infusion, this would be an underestimation of the true $AUC_{0-4\,h}$. With the gradual escalation of dose in our study, linear approximation becomes fairly plausible. The first trapezoid contributed 7 (3.3)% to the total AUC, and the error involved would be a fraction of this percentage. The portion of the AUC estimated by extrapolation was, in contrast, very small (table II).

The mean V^{ss} and terminal half-life of methohexitone in our patients agree well with values reported previously after prolonged infusions, the greater clearance in our patients giving a shorter half-life. Consequently, there is a clear difference between the results from the two long-term infusion studies and those of the bolus (or short-term infusion) studies. In the latter, the reported mean V^{ss} varied from 1.2 litre kg^{-1} [5] to 2.2 litre kg^{-1} [4], and the mean terminal half-life from 97 min [6] to 3.9 h [4]. After a bolus injection, a major portion of the drug never enters the "deep compartments" of the body, and the late half-life and the volume of distribution of methohexitone at distribution equilibrium can not be characterized adequately. The total pharmacokinetics of the drug, after a bolus injection, are determined to a large extent by slow redistribution [4]. During long-term, high-dose infusions, the "deep compartments" are loaded with drug, and their large volume contributes markedly to the observed V^{ss}. This large V^{ss}, in turn, prolongs the terminal half-life of the drug.

The mean value for unbound fraction of methohexitone in our patients (21 %) corresponds well with previous data (22 (2) %) [10]. There was no important variation in plasma protein binding between patients. Consequently, the interindividual variations in V^{ss} and clearance could not be explained by variations in plasma protein binding.

As the turnover of the 4′-hydroxy metabolite appears to be formation-rate limited, that is, its elimination half-life equals that of the parent drug, it does not accumulate in the body and probably does not cause late side-effects. Very recently, this metabolite has been shown to have only 10 % the sedative potency of methohexitone in mice [23].

The interindividual variation in clearance and V^{ss} was considerable in our patients. This parallels the large interindividual variation in the disposition of hexobarbitone found in intensive care patients [7], as a result of altered physiology.

Recovery in our patients was rapid and smooth. Post-infusion oversedation reported previously [3] occurred in patients with mean plasma concentrations of methohexitone at the end of infusion of 7.9 or 10.7 mg $litre^{-1}$—approximately twice that of our patients. Postoperative seizures occurred in three of eight neurosurgical patients after a mean plasma concentration of methohexitone, at the end of a 1-h infusion, of 18 mg $litre^{-1}$ [2]. Both these adverse effects were associated with greater plasma concentrations than those attained in our patients.

As far as can be ascertained with postoperative pyrexia as a confounding factor, the infusion of methohexitone during controlled ventilation caused little cardiovascular disturbance. This parallels earlier findings [3]: in surgical patients undergoing controlled ventilation with nitrous oxide in oxygen [1], infusion of methohexitone caused little change in arterial pressure and only a small increase in heart rate. Only during spontaneous ventilation was there marked hypotension [1]. In another study, hypotension was found to occur at a plasma concentration of at least 8 mg $litre^{-1}$ in paralysed patients [2].

Earlier data [1] show that methohexitone is not hepatotoxic. It is not likely that the hepatocellular damage in patient No. 10 was caused by interaction between enflurane and methohexitone; there was no effect of methohexitone on the kinetics of enflurane in rats when the two drugs were administered almost simultaneously [24]. In addition, enflurane does not cause induction of liver enzymes, at least not those of the mixed function oxidase subtype responsible for the metabolism of antipyrine [25].

In conclusion, methohexitone infusion for sedation of patients undergoing artificial ventilation of the lungs was tolerated well. With individual titration of the dose rate to a predetermined level of sedation, haemodynamic depression and post-infusion oversedation did not occur. The pharmacokinetics of methohexitone were very variable and pyrexia was found to have a marked effect on metabolic clearance.

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PROPOFOL AS AN I.V. ANAESTHETIC INDUCTION AGENT IN VARIEGATE PORPHYRIA

P. N. MEISSNER, G. G. HARRISON AND R. J. HIFT

SUMMARY

The choice of an i.v. anaesthetic induction poses problems for the anaesthetist confronted with a patient with one of the acute porphyrias. We undertook a prospective clinical trial in 13 variegate porphyric subjects using propofol as an anaesthetic induction agent. Urinary porphyrin precursors and porphyrins were measured before operation and 1–5 days after operation. Stool and plasma porphyrin concentrations were measured over the same period. Comparison of these data in the porphyric patients and in 21 control subjects over the trial period revealed no significant change in porphyrin or porphyrin precursor output after operation. Urinary porphyrin precursor concentrations did not exceed the limits established for variegate porphyric patients in remission, and there were no changes in the stool and plasma porphyrin profiles or any symptoms of an acute porphyric attack. We conclude that propofol did not appear to be porphyrinogenic when used for the induction of anaesthesia in 13 patients with variegate porphyria.

KEY WORDS

Anaesthetics, intravenous propofol. Complications. porphyria

The porphyrias are a group of disorders in which there is disturbance of haem biosynthesis, resulting in excessive production of haem pathway intermediates, the porphyrins and their precursors δ-aminolaevulinic acid (ALA) and porphobilinogen (PBG). The underlying abnormality may be hereditary or acquired and reflects a defect of any one of the steps of haem formation (fig. 1) [1]. The clinical features of the porphyrias are two-fold: *photocutaneous sensitivity*, caused probably by tissue accumulation of the porphyrins, and the *acute attack* [2, 3]. The latter presents with mild to severe abdominal and neuropsychiatric symptoms and may be fatal. Such an attack is often precipitated by drugs. However, patients may develop spontaneous attacks in response to stress, infections, fasting and endogenous hormonal fluctuations [4, 5]. Three types of porphyria may exhibit these acute symptoms: *acute intermittent porphyria* (AIP), *hereditary coproporphyria* (HCP) and *variegate porphyria* (VP). The acute attack is always associated with increased production and excretion of ALA and PBG [6]. These compounds are strongly implicated, therefore, in the genesis of acute symptoms, although a causal relationship has not been established unequivocally; increased urinary concentrations of ALA and PBG do serve, however, as markers of such an attack.

Although not encountered commonly, the porphyrias are of particular importance to the anaesthetist, as anaesthetic agents are among those incriminated most strongly in the precipitation of the acute attack. The i.v. induction agents in particular pose problems. The barbiturates, thiopentone and methohexitone, are extremely dangerous in porphyria [7]. Propanidid was used safely as the standard i.v. induction agent for porphyric patients for more than 25 years. One author has reported an adverse effect on porphyria [8], but propanadid has been withdrawn from use because of a high incidence of anaphylactoid reactions. Althesin, withdrawn from use for the same reason, had been shown in both animal experiments and human subjects to be porphyrinogenic [8, 9]. Testing of etomidate in

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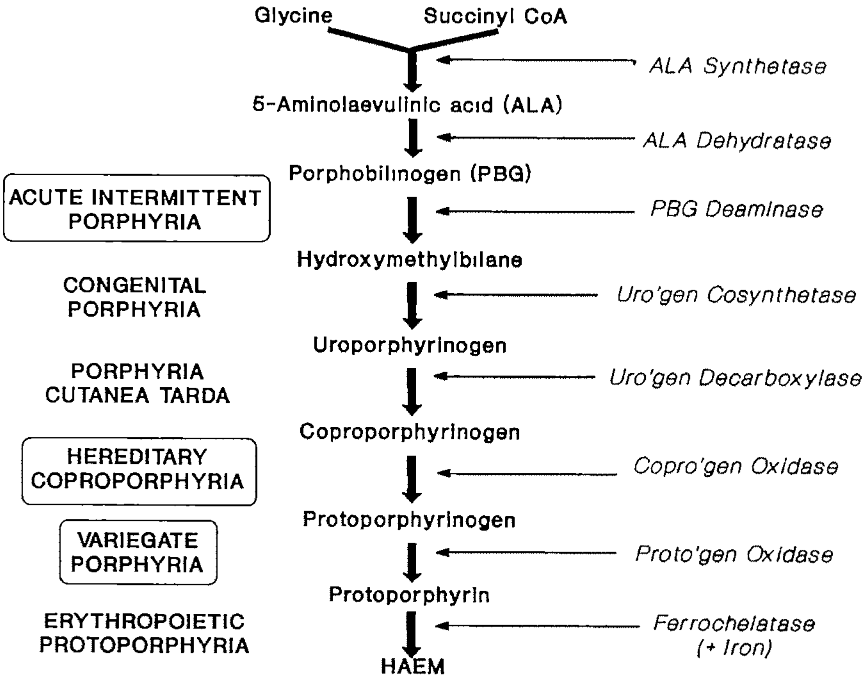

FIG. 1. The haem biosynthetic pathway, showing the enzymatic abnormalities resulting in the various types of porphyria. The three porphyrias which may exhibit acute symptoms are shown within boxes.

animal experiments also suggests porphyrinogenicity [10, 11]. Ketamine has shown no evidence of porphyrinogenicity in animal models, even after 6 h of infusion in the diethoxycarbonyl-dihydrocollidine (DDC)-primed rat model [11], but, even though it possesses excellent analgesic properties, it has other drawbacks which preclude its use as a routine induction agent.

Propofol, the most recently introduced i.v. agent, possesses many of the properties which characterize the ideal anaesthetic agent [12] and in addition, porphyrinogenicity could not be demonstrated in a rat model [13]. We report here a prospective controlled trial of propofol as an i.v. anaesthetic induction agent in porphyric subjects.

PATIENTS AND METHODS

We studied porphyric subjects (ASA grades I and II; aged 16–65 yr; normal renal function) requiring general anaesthesia for elective surgery who presented to the participating anaesthetists during a period of 1 year. As far as could be ascertained, no patient had been exposed to any porphyrinogenic drugs in their recent clinical history (past 6 months). Patients excluded from the study were those with severe underlying disease, an allergy to propofol, previous adverse experience with general anaesthesia, those undergoing operations on bladder or bowel, and those who were pregnant. These exclusion criteria were designed to ensure that there were no circumstances that could have an influence on the measurement of excreted porphyrins or precursors, or on porphyrin metabolism generally.

The diagnosis was confirmed in each patient by the demonstration of diagnostic changes in stool, urine and plasma concentrations of porphyrin. A control group was recruited consisting of people without a history of porphyria and in whom porphyrin analysis was normal. All subjects gave written, informed consent.

No restrictions were placed on the anaesthetic procedure except that induction should be with propofol and that porphyrinogenic drugs should be avoided thereafter. The mean induction dose of propofol administered to the 13 patients was 2.45 mg kg^{-1} (range 1.6–3.33 mg kg^{-1}). Thereafter, 10 received halothane and three enflurane. Atracurium or suxamethonium was used for muscle relaxation and fentanyl, alfentanil and morphine for analgesia. Patients were observed for any clinical symptoms suggestive of the acute attack for up to 5 days after anaesthesia and were asked to report any untoward developments thereafter.

Random specimens of urine were obtained before operation (day 0) and on days 1, 3 and 5 after operation. Stool and plasma specimens were obtained also, wherever possible, on the same days. All specimens were protected from light to avoid spontaneous interconversion or photodegradation of the precursors or porphyrins.

ALA and PBG were measured by an established ion-exchange technique [14] using test kits (Biorad, Munich, West Germany). Urinary, stool and plasma porphyrins were extracted, esterified, separated by thin-layer chromatography and measured by fluoroscanning, according to established methods [15–17]. Urinary concentrations of precursor and porphyrin were expressed as μmol/10 mmol creatinine and nmol/10 mmol creatinine, respectively, to take account of variability in urinary concentration. Changes in concentration of precursor or porphyrin excretion between days 0 and 1, 0 and 3, and 0 and 5 were calculated. Data from each individual patient were examined to assess whether values remained within the range of values for non-acute VP. The significance of any variation in porphyrin, ALA or PBG concentration from day 0 to day 1, 3 or 5 was assessed with Student's *t* test (two-tailed). Similarly, variations in the VP group were compared with those in the control group, as were changes in the porphyric subjects' urinary concentrations of precursor and porphyrin from day 0 to days 1, 3 and 5 compared with those in the control group.

Subjects

Only patients with VP, the most prevalent form of porphyria in South Africa, presented for surgery during the study period. Thirty-one subjects believed by their physicians to have VP were enrolled. Twelve were excluded because biochemical evidence of porphyria was lacking or because data were incomplete. A further six were excluded from analysis because, despite an abnormal porphyrin profile, the diagnosis was not established beyond doubt. In most instances this was where the diagnosis rested on a mild increase in faecal excretion of protoporphyrin alone. Thus data were obtained for 13 subjects with unequivocal VP. These were compared with 21 control subjects.

TABLE I. *Urinary ALA, PBG and total porphyrin (TP) concentrations (mean (SD))*

Group	ALA concn (μmol/10 mmol creatinine)	PBG concn (μmol/10 mmol creatinine)	TP concn (nmol/10 mmol creatinine)
Propofol controls (*n* = 21)			
Day 0	9.8 (5.8)	5.0 (3.9)	55.3 (50)
Day 1	8.9 (5.2)	5.0 (3.8)	63.8 (40)
Day 3	10.7 (4.6)	3.9 (2.4)	56.8 (39)
Day 5	11.7 (2.0)	3.5 (2.3)	70.5 (58)
Propofol VP (*n* = 13)			
Day 0	24.1 (12.9)	9.6 (7.4)	285 (243)
Day 1	26.8 (15.6)	11.4 (10.1)	371 (424)
Day 3	21.3 (12.4)	6.6 (3.9)	128 (70)
Day 5	24.4 (9.6)	9.1 (7.8)	277 (257)
Normal population (*n* = 97)			
	14.0 (12.7)	5.2 (4.4)	112 (110)
Non-acute VP population (*n* = 228)			
	29.3 (27.6)	8.1 (23.6)	473 (924)

RESULTS

It has been held traditionally that subjects with VP have normal urinary concentrations of ALA and PBG during remission. We have become aware that this is not so. We therefore redefined our normal ranges (mean, 2 SD) separately for a group of 221 subjects with VP known to be free of acute symptoms, and 93 non-porphyric subjects. These data were drawn from results from our laboratory over the past 5 years. The redefined normal ALA and PBG upper limits for VP subjects free of acute symptoms were 78 and 55 μmol/10 mmol creatinine, respectively. The upper limits for non-porphyric subjects were 40 and 14 μmol/10 mmol creatinine, respectively.

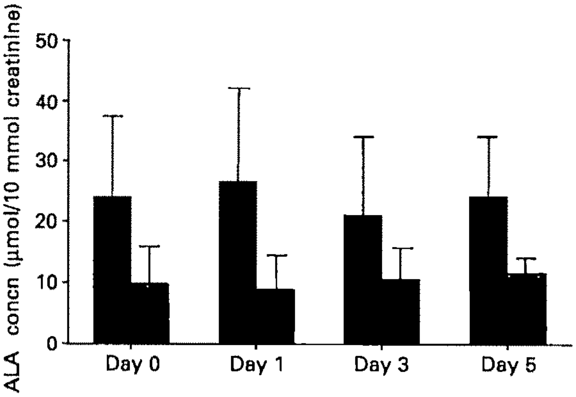

FIG. 2. Fluctuation of the mean (SD) urinary concentration of ALA for the control (▨) and porphyric (■) groups. Individual values fell within the upper limits of "normal" for each respective group at all times.

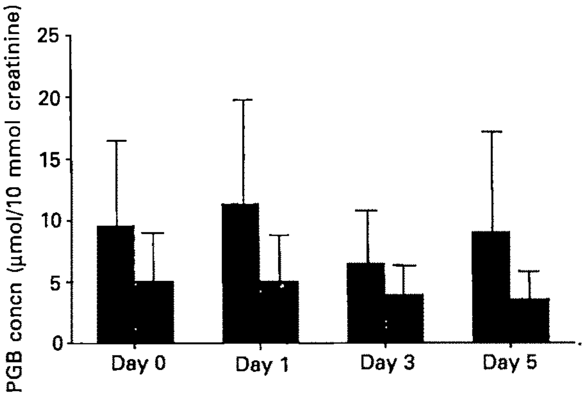

FIG. 3. Fluctuation of the mean (SD) urinary concentration of PBG for the control (▨) and porphyric (■) groups. Individual values fell within the upper limits of "normal" for each respective group at all times.

The mean concentrations of ALA, PBG and porphyrin in the porphyric patients were greater than those in the control group at all times (table I), including day 0 ($P < 0.001$), but ALA and PBG concentrations did not exceed the limits established for VP patients in remission (figs 2, 3). No significant increase in output of porphyrin or porphyrin precursor over the baseline was found after operation ($P > 0.1$); the porphyric group behaved similarly to the control group in this respect. The mean urinary concentrations of total porphyrin of the porphyric group varied greatly and were greater than those of the control group (fig. 4). Again, the change from day 0 to the postoperative days was not significant. No change in pattern of excretion of urinary porphyrin to the earlier haem pathway intermediates was demonstrated by thin-layer chromatography (data not shown). Such a shift would be expected if the pathway were stressed. There were no changes in stool and plasma porphyrin profiles (data not shown).

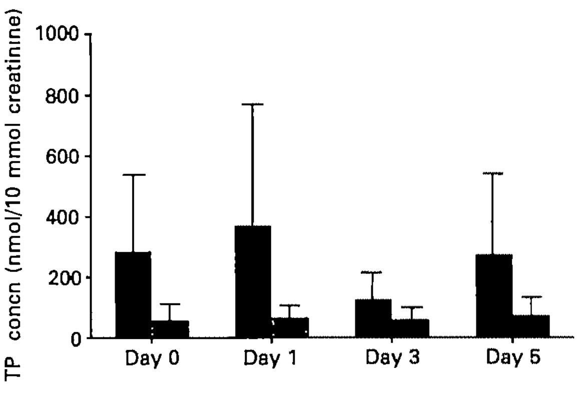

FIG. 4. Fluctuation of the mean (SD) urinary concentration of total porphyrin (TP) for the control (▨) and porphyric (■) groups. The concentrations in the porphyric group are high, indicative of the underlying porphyric status of the VP patients.

No symptoms suggestive of an acute attack of porphyria were noted in any subject at any stage.

DISCUSSION

To be considered safe for use in the acute porphyrias, ideally a drug should meet the following criteria: first, it should not cause increase in production of porphyrin or porphyrin precursor, and should not induce ALA synthetase or diminish free haem concentrations in laboratory test systems, including various types of cell culture [6, 18–20] and laboratory animals rendered porphyric by the administration of agents such as DDC [6, 9, 21, 22]; second, the drug should be devoid of porphyrinogenic potential in human subjects—its administration should not be followed by symptoms of the acute attack or by a significant increase in excretion of porphyrin and precursor. Such data are usually derived from personal experience, anecdotal evidence or from individual case reports. Few, if any, drugs have had porphyrinogenicity tested prospectively in controlled trials in porphyric patients. Thus doctors must often base their decision to use a particular drug in a porphyric subject on incomplete or possibly inaccurate data. Also, experience in human subjects and laboratory testing sometimes give conflicting results [6, 8, 23].

Propofol has been reported not to induce hepatic ALA synthetase in the rat [13] and therefore, by implication, to be non-porphyrinogenic, but it induces hepatic ALA synthetase in DDC-primed chick embryos [20 and personal communication, Deybach JC]. However, this system is considered by some to be extremely sensitive and may produce seemingly false positive results [6]. There have also been conflicting reports on its safety in humans. In one study, propofol was used to induce anaesthesia in a patient with AIP with apparent safety [24], whereas another case report indicated that urinary concentrations of porphyrin and PBG increased in a VP patient anaesthetized with propofol [25]. However, this patient had been exposed to several anaesthetics over a few days, including an infusion of propofol, and the changes in concentrations of porphyrin and PBG were unconvincing [26, 27]. The patient did not experience acute symptoms.

This study represents a clinical trial undertaken to assess the safety of propofol for the induction of anaesthesia in patients with an acute porphyria. The lack of significant increase in concentrations of ALA and PBG following administration of propofol suggests that the drug has low porphyrinogenic potential in porphyric subjects, at least when used in the dose and manner reported here. This is supported further by failure to alter the urinary, stool and plasma profiles of porphyrin either quantitatively or qualitatively. No symptoms suggestive of the acute attack were noted. We conclude, therefore, that propofol, as used for the induction of anaesthesia in 13 patients with VP, did not appear to be porphyrinogenic. However, the number of patients studied was small and the disease is unpredictable, so care should always be taken when using *any* drug in porphyria. We cannot extrapolate our findings to the use of propofol for maintenance of general anaesthesia by continuous infusion until further clinical experience has been obtained. In the light of the case report referred to above [25], we suggest that caution be exercised with propofol for this purpose.

Comment is necessary on the choice of halothane for maintenance of anaesthesia in this study. Two reports and some experimental data warn of its risk in porphyric patients [7, 20, 28], but this conflicts with other experimental data [10] and much clinical experience accumulated by our and other units, where it has been used safely in porphyric patients on numerous occasions. As 10 of our patients received halothane, this study presents substantial evidence that halothane, in addition to propofol, may be used safely in the acute porphyrias.

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EFFECT OF I.V. ANAESTHESIA WITH PROPOFOL ON DRUG DISTRIBUTION AND METABOLISM IN THE DOG

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SUMMARY

We have studied the effect of i.v. anaesthesia with propofol in the emulsion (Intralipid) formulation on drug distribution and metabolism in six dogs using dual-route administration of propranolol as a model compound. Each dog was studied on two consecutive days: day 1 awake and day 2 during propofol anaesthesia (6 mg kg^{-1} followed by an infusion of 0.8 mg kg^{-1} min^{-1}). Propofol anaesthesia was associated with reduced intrinsic clearance by 40% ($P < 0.05$) but no significant difference in systemic clearance or hepatic plasma flow. Propofol produced marked changes in drug distribution; volume of distribution (V^{ss}) of propranolol increased 54% from 82.5 (SEM 7.3) litre awake to 127.3 (27) litre during propofol anaesthesia ($P < 0.05$). This change was accompanied by an increase ($P < 0.05$) in the free fraction of propranolol from 8.5 (0.7)% in awake to 14.0 (0.7)% in propofol-anaesthetized dogs. The combination of the effects of both drug clearance and protein binding resulted in a 65% decrease in the intrinsic clearance of unbound drug ($P < 0.05$). In contrast with the effects of propofol on drug distribution, infusion of Intralipid alone in another group of six dogs had no significant effects on drug distribution, protein binding or drug metabolism. We conclude that propofol is a modest inhibitor of drug metabolism, but has major effects on propranolol distribution, possibly by changing plasma protein binding.

KEY WORDS

Anaesthetics, intravenous: propofol Biotransformation: propranolol Pharmacology drug interaction, propofol, propranolol

Propofol is an i.v. anaesthetic agent with pharmacokinetic properties (rapid clearance and hence relatively short duration of action) that make it suitable for maintenance of anaesthesia by continuous i.v. infusion. Propofol is formulated as an emulsion in Intralipid (2,6 diisopropyl phenol in 10% soybean oil, 1.2% phospholipids, 2.25% glycerin and water), which is one of the most widely used sources of fat for total parenteral nutrition.

It is now well recognized that anaesthesia and surgery cause profound changes in perioperative drug disposition; previous studies have shown that both inhalation anaesthetics (halothane, enflurane and isoflurane) and a fentanyl–nitrous oxide technique inhibit drug metabolism [1–3]. Reductions in hepatic blood flow may contribute also to reduced drug clearance during anaesthesia.

This study was designed to investigate the effects of total i.v. anaesthesia with propofol on drug disposition in the dog, using propranolol as a model compound. In addition, as propofol is administered frequently in intensive care units to provide sedation and Intralipid is used also in the same setting, we studied the effects of Intralipid on drug distribution and metabolism.

METHODS

The study was approved by the Animal Care Committee of the Vanderbilt University Division of Animal Care.

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Six healthy male mongrel dogs (mean weight 24.8 (SEM 1.9) kg) were studied on two consecutive days. Cannulae were inserted into the femoral artery, femoral vein and portal veins in each dog under pentobarbitone anaesthesia (30 mg kg^{-1} i.v.) 7 days before the first study day. Identical pharmacokinetic studies were performed in each dog on two consecutive days; on the first, the study was performed in awake dogs which received an i.v. infusion of 5% glucose solution. Twenty-four hours later, the study was repeated during propofol anaesthesia. In another group of six dogs (mean weight 26.6 (0.6) kg) the disposition of propranolol was measured during a continuous i.v. infusion of 5% glucose solution on the first study day followed 24 h later, on the second day, by a continuous i.v. infusion of Intralipid.

Anaesthetic technique

On the first study day, an infusion of 5% glucose 4.8 ml kg^{-1} h^{-1} was given to awake dogs via the femoral vein cannula. The pharmacokinetic study was performed after 1 h of infusion and the infusion was continued for the duration of blood sampling. Twenty-four hours later, the pharmacokinetic study was repeated during total i.v. anaesthesia with propofol in the emulsion formulation. Anaesthesia was induced with an i.v. dose of propofol 6 mg kg^{-1} and maintained with an i.v. infusion of propofol via the femoral vein at a rate of 0.8 mg kg^{-1} min^{-1} (4.8 ml kg^{-1} h^{-1}) [4]. Following tracheal intubation, the lungs were ventilated artificially ($FI_{O_2} = 1$) to maintain end-tidal carbon dioxide concentrations within the physiological range (Pa_{CO_2} 4.6–5.3 kPa) using a Datex anaesthetic monitor (Datex Medical Instrumentation, Inc., MA 01876 U.S.A.). Systemic arterial pressure was measured continuously via the femoral artery cannula. The pharmacokinetic study was commenced after 1 h of administration of propofol.

For the Intralipid study, on the first day the dogs received an i.v. infusion of 5% glucose via the femoral vein cannula at a rate of 4.8 ml kg^{-1} h^{-1}. After 1 h of infusion, the pharmacokinetic study was commenced. Twenty-four hours later, the pharmacokinetic study was repeated during administration of Intralipid via the femoral vein cannula at a rate of 4.8 ml kg^{-1} h^{-1} . The pharmacokinetic study was commenced again after the infusion had been administered for 1 h.

Pharmacokinetic study

The same pharmacokinetic technique was performed on each dog on both study days. Tritiated propranolol 200 μCi (specific activity 67 mCi mg^{-1}, Amersham Searle Corp., Arlington Heights, Il) was injected into the femoral vein over 1 min, and simultaneously 40 mg of unlabelled propranolol was infused into the portal vein over a 10-min period by constant infusion pump. The intraportal route was chosen to bypass the variable absorption which may occur after oral administration and which might be affected also by propofol anaesthesia. Arterial blood samples (4 ml) were taken 2, 4, 6, 8, 10 and 15 min after completion of the infusion, and then at 15-min intervals for the next 3.75 h. Each blood sample was replaced by twice its volume of 0.9% saline solution. Plasma concentrations of unlabelled propranolol were measured by high pressure liquid chromatography (HPLC) and the ^{3}H-propranolol plasma concentrations by liquid scintillation counting of the HPLC eluant corresponding to each eluant peak [5]. Plasma samples were obtained also on each study day immediately before the commencement of administration of propranolol for the measurement of propranolol plasma binding by equilibrium dialysis [6].

Pharmacokinetic calculations

Propranolol clearance (Cl) following systemic (Cl_s) and portal (Cl_p) administration were calculated as:

$$Cl = \text{dose}/\text{AUC}$$

where dose = dose of either ^{3}H-propranolol given i.v. or unlabelled propranolol given intraportally, and AUC = area under the time–concentration curve (extrapolated to infinity) calculated by the trapezoidal rule for either ^{3}H-propranolol ($AUC_{i\,v}$) or unlabelled propranolol (AUC_p). As propranolol is metabolized only in the liver and was infused into the portal vein (equivalent to 100% oral absorption), the clearance of the intraportal propranolol (Cl_p) is numerically equal to the total intrinsic clearance of propranolol (Cl_{int}), assuming a "well stirred" model of hepatic drug clearance [7]. The latter reflects the intrinsic capacity of the hepatic drug metabolizing enzyme system and is independent of hepatic blood flow. The clearance of unbound drug (free clearance) was calculated by dividing total clearance by free fraction.

The systemic elimination rate constant (k_{10}) was calculated by linear regression analysis of the terminal phase of the time–concentration curve for ^{3}H-propranolol, and systemic elimination half-life ($T_{\frac{1}{2}}$) was calculated as:

$$T_{\frac{1}{2}} = 0.693/k_{10}$$

Volume of distribution (V^{ss}) was then calculated as:

$$V^{ss} = Cl_s[\mathrm{AUMC}/\mathrm{AUC}]$$

where AUMC is the area under the first moment curve.

Mean hepatic plasma flow was calculated as follows: after intraportal administration of a drug of dose D_p, the amount of drug entering the systemic circulation is equal to $F.D_p$ where F is the fractional systemic availability. Thus:

$$Cl_s = F.D_p/\mathrm{AUC}_p$$

But

$$Cl_p = D_p/\mathrm{AUC}_p$$

therefore

$$Cl_s = F.Cl_p$$

and

$$F = 1 - E$$

where E is the hepatic extraction ratio.

Therefore

$$Cl_s = (1-E)\ Cl_p$$

Also, by the Fick principle:

$$Cl_s = Q.E$$

where Q is the apparent hepatic plasma flow. Thus, substituting for E:

$$Q = Cl_s.Cl_p/(Cl_p - Cl_s)$$

Statistical analysis

Statistical comparisons were performed using Student's *t* test for paired data, and $P < 0.05$ was taken as the minimum level of statistical significance. Data are expressed as mean (SEM).

RESULTS

Mean plasma concentrations of propranolol following intraportal and i.v. administration are shown in figure 1. Propofol anaesthesia significantly reduced intrinsic clearance of propranolol from 3.3 (0.6) litre min^{-1} during infusion of glucose in awake dogs to 2.0 (0.4) litre min^{-1} during propofol anaesthesia (fig. 2), indicating that propofol anaesthesia inhibited propranolol metabolism. However, propofol anaesthesia had no effect on systemic clearance calculated from total (bound+free) (0.75 (0.1) litre min^{-1} during infusion of glucose; 0.68 (0.07) litre min^{-1} during propofol anaesthesia) or mean hepatic plasma flow with a mean hepatic plasma flow of 1.01 (0.11) litre min^{-1} in awake dogs and 1.08 (0.1) litre min^{-1} during propofol anaesthesia (fig. 2).

Propofol anaesthesia produced marked changes in drug distribution (fig. 3). The volume of distribution (V^{ss}) of propranolol increased 54%

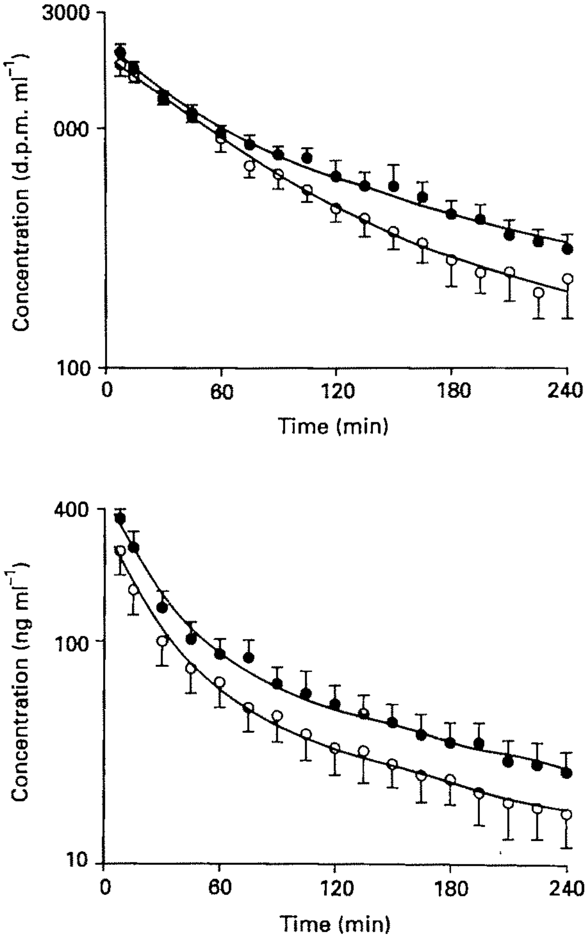

FIG. 1. Plasma concentrations of propranolol (mean, SEM) after (top panel) i.v injection of ^{3}H-propranolol 200 µCi and after (bottom panel) the intraportal infusion of racemic propranolol 40 mg. ○ = Day 1· control, awake; ● = day 2: propofol anaesthesia.

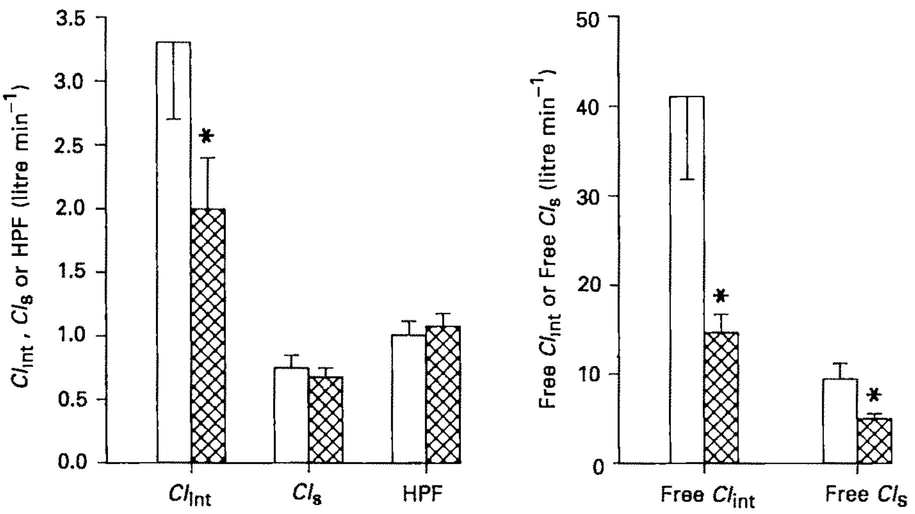

FIG. 2. Effect of propofol anaesthesia on the intrinsic clearance of propranolol (Cl_{int}), systemic clearance of propranolol (Cl_s) and hepatic plasma flow (HPF) (left hand panel). Effect of propofol on free intrinsic clearance of propranolol (Free Cl_{int}) and free systemic clearance of propranolol (Free Cl_s) (right hand panel). □ = Day 1: awake; ☒ = day 2: propofol anaesthesia. Values are mean, SEM. $^*P < 0.05$.

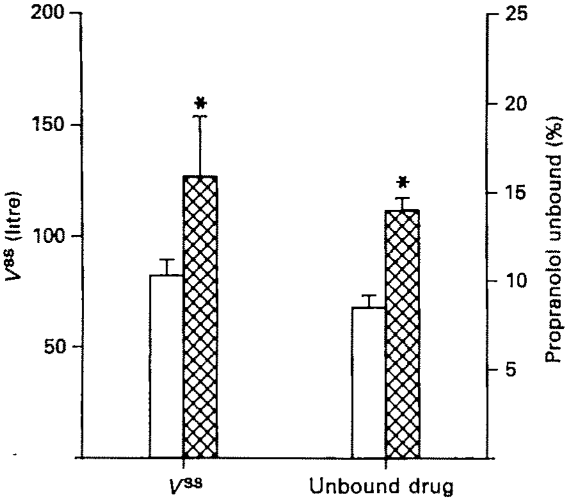

FIG. 3 Effect of propofol anaesthesia on plasma binding and volume of distribution (V^{ss}) of propranolol. □ = Day 1: awake; ☒ = day 2: propofol anaesthesia Values are mean, SEM. $^*P < 0.05$.

from 82.5 (7.3) litre in awake dogs to 127.3 (2.7) litre during propofol anaesthesia ($P < 0.05$). This was accompanied by an increase ($P < 0.05$) in the free fraction of propranolol from 8.5 (0.7)% in awake dogs to 14.0 (0.7)% in propofol-anaesthetized dogs. There was a significant correlation ($r = 0.64$; $P < 0.05$) between the volume of distribution and the free fraction of propranolol.

The combination of the effects of propranolol on protein binding and on drug clearance resulted in marked effects on the clearance of unbound drug (fig. 2). There was a 65% reduction in the clearance of unbound drug (Cl_{int}) following portal administration from 41.1 (9.3) litre min^{-1} awake to 14.7 (2.0) litre min^{-1} during propofol ($P < 0.05$). The free systemic clearance (free Cl_s) decreased by only 47%, from 9.5 (1.7) to 5.1 (0.6) litre min^{-1} ($P < 0.05$) (fig. 2).

In contrast with the effects of propofol anaesthesia on drug distribution and metabolism, infusion of Intralipid had no significant effects on the disposition of propranolol (figs 4, 5). There was no significant difference in volume of distribution of propranolol and the plasma binding of propranolol on both study days.

DISCUSSION

This study has demonstrated that propofol anaesthesia produced a 40% reduction in the intrinsic clearance of propranolol and a 65% reduction in the clearance of free drug, implying that propofol inhibited drug metabolism. Propranolol concentrations following intraportal administration were greater during propofol anaesthesia than when the animals were conscious.

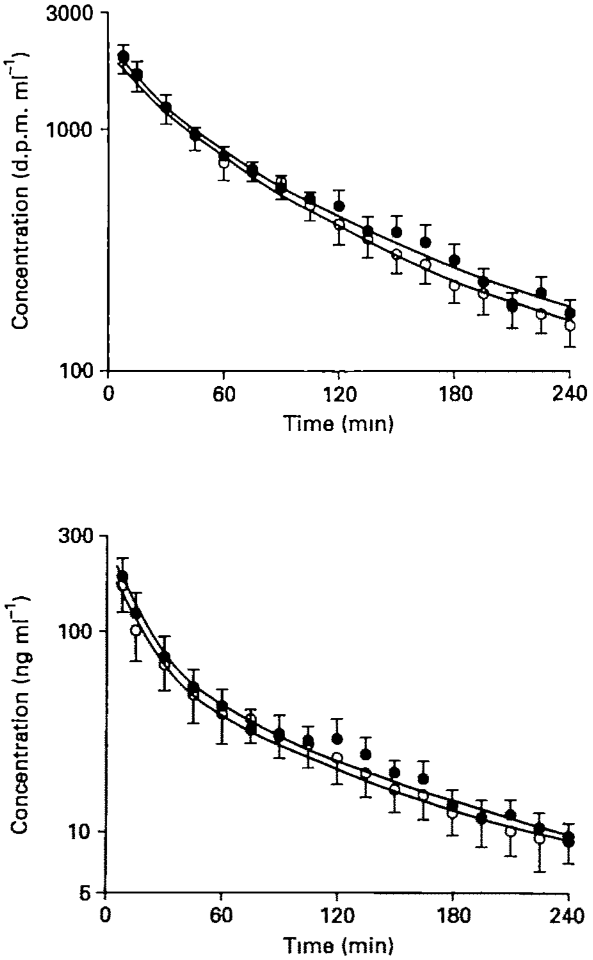

FIG. 4. Plasma concentrations of propranolol (mean, SEM) after (top panel) i.v. injection of ^{3}H-propranolol 200 µCi and after (bottom panel) the intraportal infusion of racemic propranolol 40 mg. ○ = Day 1: control, glucose, awake; ● = day 2: Intralipid, awake.

However, although concentrations of propranolol after systemic administration tended to be greater during propofol anaesthesia than in awake animals, propofol anaesthesia did not produce a significant change in the area under the concentration–time curve (AUC), and hence in systemic clearance for total drug. However, when the change in protein binding was taken into account, propofol produced a 47% reduction in the systemic clearance of unbound drug.

When a drug is administered orally or via the intraportal route, clearance is independent of liver blood flow, equals intrinsic clearance [7] and is thus dependent on the drug metabolizing enzyme capacity of the liver. However, when a drug of high extraction such as propranolol is administered systemically, the kinetics become blood-flow dependent. In the present study, propofol produced no change in hepatic plasma flow, and thus, although we found a significant change in intrinsic clearance, this was not the case for total systemic clearance.

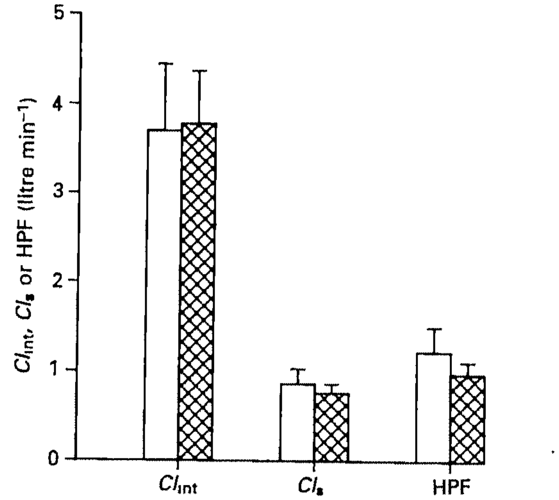

FIG. 5. Effect of Intralipid on the intrinsic clearance of propranolol (Cl_{int}), systemic clearance of propranolol (Cl_s) and hepatic plasma flow (HPF). □ = Day 1: control, glucose; ⊠ = day 2: Intralipid.

Propofol is a relatively modest inhibitor of drug metabolism compared with the profound inhibition of metabolism demonstrated previously for the volatile anaesthetics [3, 8]. We have shown previously that enflurane reduced the intrinsic clearance of propranolol under similar experimental conditions by more than 70% [1]. In contrast, spinal anaesthesia does not appear to affect propranolol metabolism [9] and hence intrinsic clearance, systemic clearance or elimination half-life [9, 10]. Thus propofol anaesthesia produces significant but relatively modest effects on drug metabolism.

In common with many drugs, propranolol is administered clinically as a racemic mixture and the (−) enantiomer is 100 times more potent as a β-adrenergic blocking agent than the (+) enantiomer in humans. In dogs, the (−) enantiomer has a greater systemic clearance and a lower oral bioavailability than the (+) enantiomer. We have shown previously that halothane-induced inhibition of propranolol metabolism is stereoselective, resulting in proportionally greater concentrations of (−) propranolol during halothane anaesthesia than are present in awake dogs [11]. Thus, as propranolol is administered as a racemate, the effects of propofol on propranolol metabolism might differ also for the two enantiomers.

Our data also show that propofol anaesthesia had major effects on propranolol distribution, producing a decrease in plasma binding and an increase in percentage of free drug which resulted in an increase in volume of distribution. It is possible, therefore, that important protein-binding displacement interactions may occur acutely during i.v. anaesthesia with propofol. It is interesting that, although drug volume of distribution may be acutely reduced during inhalation anaesthesia, resulting in greater concentrations, these changes are not caused by changes in protein binding [12]. Volatile anaesthetics have been shown to have small but probably clinically insignificant effects on drug binding [2, 12, 13]. The combination of the propofol-induced changes in protein binding coupled with the changes in clearance resulted in even more marked effects on the clearance of unbound drug in the present study.

As propofol is such a highly protein bound [14] and lipid soluble drug with a high clearance in addition, it might be predicted that the co-adminstration of opioids as premedicants, neuromuscular blocking agents, antibiotics and other anaesthetics may alter the pharmacokinetic profile of propofol. Pharmacokinetic interactions have been demonstrated previously for fentanyl and propofol. It has been shown that, when propofol and fentanyl are co-administered, propofol concentrations are greater in patients pretreated with fentanyl than in patients anaesthetized with nitrous oxide without fentanyl [15]. A pharmacokinetic interaction between propofol and alfentanil has also been demonstrated [16]. Although alfentanil does not appear to interfere with the pharmacokinetic profile of propofol, propofol anaesthesia results in greater than predicted concentrations of alfentanil.

Alteration in the degree of protein binding has important pharmacokinetic and pharmacodynamic implications, as it is the unbound moiety that crosses biological membranes and produces a pharmacological effect [17]. Alteration in plasma binding may affect drug distribution, elimination half-life and organ clearance [17]. The effect of protein binding on hepatic clearance depends on the extraction ratio of the drug in question; for a drug of moderately high extraction such as propranolol, clearance is flow-dependent and changes in plasma binding have little influence on hepatic clearance following systemic administration for propranolol. This is illustrated well in this study, in which total Cl_s was unchanged where free Cl_s was decreased by 47%. The effect of displacement from protein binding sites on drug concentration depends on whether or not elimination is unrestricted by protein binding or is restricted (low extraction). For the former, an increase in free fraction caused by displacement results in an increase in volume of distribution and a decrease in total concentration. With continued administration, as clearance is unaffected by protein binding, the total concentration returns to predisplacement values, resulting in an increase in free concentration. The possibility of increased pharmacological effects is therefore present. Such an effect can be seen in the present study when the free concentration after intraportal administration was 280% greater after propofol, as a result of the combination of both change in drug metabolism and change in protein binding. For a restrictively eliminated drug, after displacement, the free fraction increases and again the total plasma concentration decreases. However, in contrast with continued administration, the greater free fraction results in increased clearance, so that the total concentration decreases, but the increased clearance restores the free concentration to predisplacement values. There is thus no persisting change in pharmacological effect or toxicity.

Many factors affect drug metabolism, and it is likely that changes in drug metabolism may contribute to altered drug response in patients in the intensive care unit [18, 19]. These patients often require parenteral nutrition. Healthy volunteers administered an i.v. nutritional regimen of amino acids (Aminosyn 3.5%) exhibit an acute increase in antipyrine metabolism (an index of oxidative drug metabolizing activity), indicating that rates of drug elimination may change rapidly in seriously ill patients receiving total parenteral nutrition [20, 21]. Intralipid is a fat emulsion used widely for total parenteral nutrition, and the present study has shown that the administration of the Intralipid emulsion had no effect on propranolol metabolism in dogs. Although we cannot speculate on the effect of Intralipid on drug metabolism in humans, the effect of propofol on drug metabolism is clearly not attributable to the fat emulsion formulation.

ACKNOWLEDGEMENTS

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PRIMING OF CARDIOPULMONARY BYPASS WITH HUMAN ALBUMIN OR RINGER LACTATE: EFFECT ON COLLOID OSMOTIC PRESSURE AND EXTRAVASCULAR LUNG WATER

A. HOEFT, H. KORB, U. MEHLHORN, H. STEPHAN AND H. SONNTAG

SUMMARY

We have undertaken a randomized study on 20 patients undergoing coronary artery bypass surgery in order to determine the influence of cardiopulmonary pump prime solutions on colloid osmotic pressure and extravascular lung water. Crystalloid priming with Ringer lactate was compared with an albumin solution of nearly physiological colloid osmotic composition (4%). Measurements of extravascular lung water were performed by a modified, highly sensitive thermal dye technique, with additional detection of tracer signals in the pulmonary artery. In the Ringer lactate group, a significantly greater decrease in colloid osmotic pressure occurred immediately after onset of cardiopulmonary bypass. The more pronounced decrease in colloid osmotic pressure and in transcapillary gradient (difference between colloid osmotic pressure and pulmonary capillary wedge pressure) in the Ringer lactate group was associated with a significant increase in extravascular lung water (by 60%) in the postoperative period; the human albumin group, however, showed only a slight tendency to increased lung water. There were no differences in haemodynamic or respiratory states after operation.

KEY WORDS

Blood· colloid osmotic pressure Lung extravascular water Surgery: cardiopulmonary bypass, priming solution

One factor which might contribute to respiratory dysfunction after open heart surgery is accumulation of extravascular lung water [1–9]. The intravascular colloid osmotic pressure is an important determinant of transcapillary fluid movement and therefore should be maintained in the physiological range, in particular when capillary permeability is increased [10]. However, with the onset of cardiopulmonary bypass, the plasma is diluted by the prime volume of the machine and colloid osmotic pressure may decrease considerably, depending on the composition of the priming solution [1, 2, 6, 11–14]. Addition of colloids to the pump prime solution has been advocated, therefore, by several groups. However, in most studies the added amounts of albumin or hydroxyethyl starch were not sufficient to result in a physiological colloid osmotic pressure in the prime solutions [1, 11–14]. Furthermore, the results on postoperative accumulation of extravascular lung water were controversial: while some studies failed to show an increase in lung water [12], others demonstrated a significant increase in lung water at different times after operation [13, 15, 16].

The aim of this study was to compare the effect of a high colloid osmotic priming solution (4% albumin) with a pure crystalloid priming solution (Ringer lactate) on postoperative extravascular lung water. In addition, we examined the time at which water was most likely to accumulate in the postoperative period by frequent measurements using a newly developed, sensitive method for measurement of lung water with detection of dye and temperature time courses in the pulmonary artery in addition to the aorta.

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PATIENTS AND METHODS

We studied 20 patients undergoing aortocoronary venous bypass surgery. The study was approved by the Committee for Medical Ethics of the University and accepted by the German Research Foundation, SFB 330-Organ Protection. Each patient gave full informed consent at the time of the preoperative visit. No patient had a history of congestive heart failure or valvular heart disease. All patients had ejection fractions greater than 50%.

Patients were premedicated with flunitrazepam 2 mg orally 1 h before arrival in the operating room. When leaving the ward they received additionally promethazine 50 mg and piritramide 15 mg i.m. When they arrived in the operating room, ECG leads were attached; under local anaesthesia the left radial artery was cannulated and a central venous catheter was inserted via the left cubital vein. General anaesthesia was induced with fentanyl 0.5 mg and etomidate 20 mg, and pancuronium 8 mg was given to facilitate tracheal intubation. Artificial ventilation was maintained with an FI_{O_2} of 0.5 in air or in nitrous oxide when systolic arterial pressure exceeded 100 mm Hg.

Patients were allocated randomly to two groups. In one group (Ringer lactate (RL) group) ($n = 10$) crystalloid solutions only were used for priming of the cardiopulmonary bypass: a 2000-ml solution contained Ringer's lactate 1400 ml, 5% glucose 500 ml and bicarbonate 100 ml. The second group (human albumin (HA) group) ($n = 10$) also received a 2000-ml priming solution, in which 400 ml of Ringer's lactate was replaced by 20% human albumin 400 ml, producing a concentration of 4% human albumin in this priming solution (table I). In all patients a membrane oxygenator was used (Maxima, Medtronic).

After induction of anaesthesia, a specially designed balloon-tipped catheter with an additional fibreoptic lead for intravascular dye measurements was placed into the pulmonary artery via the right internal jugular vein. A second combined fibreoptic–thermistor catheter was inserted into the left femoral artery and advanced into the aorta to the thoracic part of the descending aorta (fig. 1). Arterial and mixed venous blood samples were obtained for measurement of haemoglobin and oxygen content and colloid osmotic pressures (IL 186 Weil Oncometer, semipermeable membrane with 95% rejection of albumin). In addition to standard haemodynamic variables (heart rate, pulmonary and aortic pressures), extravascular lung water, central blood volume and cardiac output were measured by a double indicator dilution technique [17, 18]: 10 ml of an ice cold dye bolus (indocyanine green 12.5 mg) was injected into the proximal lumen of the pulmonary artery catheter. The resulting dye and temperature dilution curves in the pulmonary artery and aorta were detected by the fibreoptic–thermistor catheters, which were connected to special optoelectronic devices (IVS 4000, Fa. Schwarzer, München, FRG). The analog signals

TABLE I. *Components of the priming solutions: crystalloid with only Ringer's lactate (RL), and 4% human albumin (HA) solution*

Component	RL ($n = 10$)	HA ($n = 10$)
20% Human albumin (ml)	—	400
Ringer's lactate (ml)	1400	1000
5% Glucose (ml)	500	500
Bicarbonate (ml)	100	100
Total (ml)	2000	2000

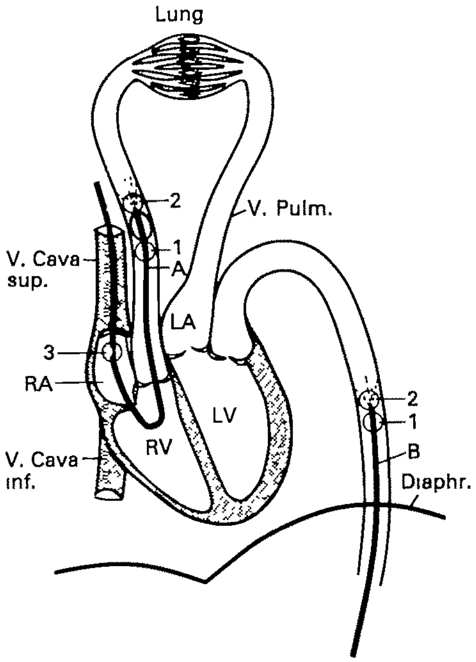

FIG. 1. Positions of the combined fibreoptic–thermistor catheters in the pulmonary artery (A) and the thoracic aorta (B). Temperature and dye measuring sites are 1 and 2, respectively The ice cold dye bolus was injected into the proximal lumen of the pulmonary artery catheter (3). LA/RA = Left/right atrium; LV/RV = left/right ventricle; V. Cava sup. = superior vena cava; V. Cava inf. = inferior vena cava; V. Pulm. = pulmonary vein; Diaphr. = diaphragm.

of the curves were digitized on-line and stored on hard disk by an IBM-compatible computer. Measurements were performed after induction of anaesthesia (a.A), after cannulation for cardiopulmonary bypass (a.C), during cardiopulmonary bypass (I-IV CPB), after decannulation (a.CPB), at the end of surgery (ES) and 1, 2, 3, 4, 5, 6, 9, 12 and 24 h after operation.

Cardiac output was measured from aortic and pulmonary thermodilution curves according to the Stewart Hamilton procedure. The average of both values was used for further calculations.

Conventionally, measurement of extravascular lung water is based on calculation of mean transit times for dye and heat from aortic dilution curves. This is possible only after elimination of indicator recirculation by monoexponential extrapolation [11–16]. This approach involves assumptions that have not been verified [19] and have been shown in animal experiments to bear a systematic additive error and possess limited accuracy [18]. In contrast, we chose a more complex mathematical approach, which eliminates the effects of indicator recirculation by additional measurement of tracer signals in the pulmonary artery. Thus assumptions about the indicator kinetics at the entrance to the pulmonary system, including the possibility of recirculating indicator, are not required. The theoretical principles of this technique have been described in more detail in previous publications from our group [17–18] and by Zierler [19]. In brief, a mathematical algorithm termed the "convolution integral" is used for numerical description of the tracer passage through the vascular bed of the lung:

$$c_{\mathrm{ao}}(t) = \int_0^t h(t-u)\, c_{\mathrm{pulm}}(u)\, \mathrm{d}u \qquad (1)$$

The convolution integral (equation (1)) describes the concentration–time course of an aortic tracer curve ($c_{\mathrm{ao}}(t)$) depending on the tracer concentration–time course in the pulmonary artery ($c_{\mathrm{pulm}}(t)$) and indicator dispersion during lung passage specified by a transport function ($h(t)$; u is a dummy variable for integration). This transport function may be considered the aortic concentration–time course of a tracer, which would result after an ideal indicator bolus (infinite short duration without any recirculation) is injected into the pulmonary artery.

In the present study the transport functions for temperature and dye were determined by iterative convolution of the pulmonary artery dye and temperature dilution curves with a lagged normal density function [20]. This function has been shown previously to represent an accurate model for physiological tracer dispersion in the pulmonary vascular system [21]. A non-linear least square procedure was used to perform the iterative convolution of the curves and to adjust the parameters of the lagged normal density function until the best fit of computed and measured aortic tracer kinetics was achieved [22]. The mean transit times, which are essentially necessary for calculation of extravascular lung water, may then be derived algebraically from the calculated parameters of the function without extrapolation procedures [20, 21]. Total lung water (including intravascular water) and pulmonary blood volume may be calculated from the product of cardiac output with the mean transit times of heat and protein bound dye, respectively. Extravascular lung water is the difference between total lung water and pulmonary blood volume.

Statistics

Two-tailed Student's t tests for unpaired data were used to compare patient data. The effects of colloid and crystalloid priming solution on all measured data were compared by two-way analysis of variance for repeated measures (ANOVA). If differences between the two groups were significant ($P < 0.05$), *post hoc* comparisons were performed using the Tukey HSD test with a level of significance $P < 0.05$. All calculated P values are two-tailed. All group data are reported as means (SD).

TABLE II. *Patient data and data on cardioplegia, extracorporeal circulation and ischaemic arrest in the Ringer's lactate (RL) and human albumin (HA) groups (means* (SD)*). No statistically significant differences between groups were observed* (t *test for unpaired data*)

	RL ($n = 10$)	HA ($n = 10$)
Age (yr)	55.1 (5.6)	56.8 (6.4)
Body weight (kg)	74.0 (11.8)	78.1 (11.8)
Height (m)	1.71 (0.07)	1.72 (0.08)
Body surface area (m^2)	1.89 (0.18)	1.95 (0.18)
Number of coronary anastomoses	2.7 (0.67)	3.1 (1.01)
Total amount of cardioplegia solution (ml)	2075 (109)	2212 (555)
Duration of ischaemic arrest (min)	56.2 (18.4)	76.0 (36.8)
Duration of extracorporeal circulation (min)	97.9 (25.7)	116.0 (52.6)
Time end surgery to extubation (h)	20.2 (6.1)	19.2 (6.8)

RESULTS

There were no differences between the two groups of patients in general characteristics, time of ischaemic arrest and extracorporeal circulation or cardioplegia (table II). Arterial and pulmonary arterial pressures, heart rate and body temperature showed the same time courses for both groups (data not presented). With the onset of extracorporeal circulation, colloid osmotic pressure decreased by more than 50% (from 18.4 (SD 1.3) mm Hg to 9.0 (0.8) mm Hg) with crystalloid solutions (RL group); in the HA group the decrease in colloid osmotic pressure was signifi-

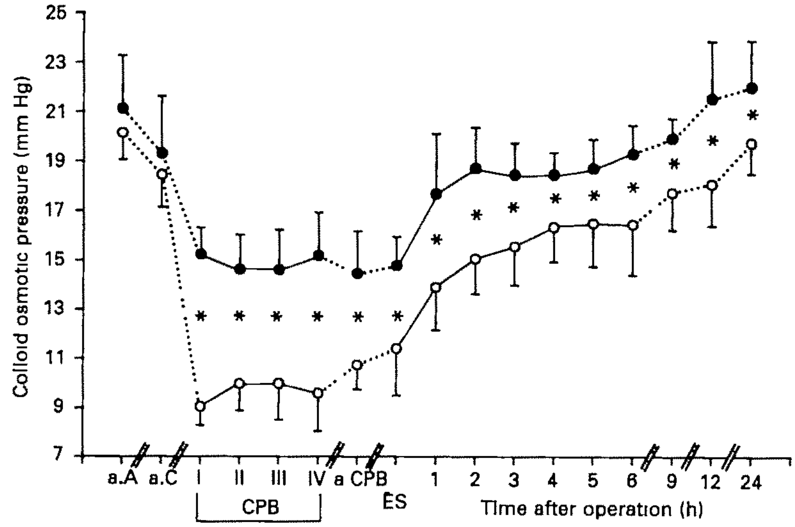

FIG. 2. Time course of colloid osmotic pressure in the Ringer's lactate (RL) (○) (*n* = 10) and human albumin (HA) (●) (*n* = 10) groups (mean, SD). After onset of cardiopulmonary bypass, COP decreased by more than 50% in the RL group, compared with 30% in the HA group ($P < 0.001$ for ANOVA overall differences between groups). The difference between both groups remained significant for the first 24 h after the end of surgery. *$P < 0.05$ for Tukey HSD *post hoc* comparison.

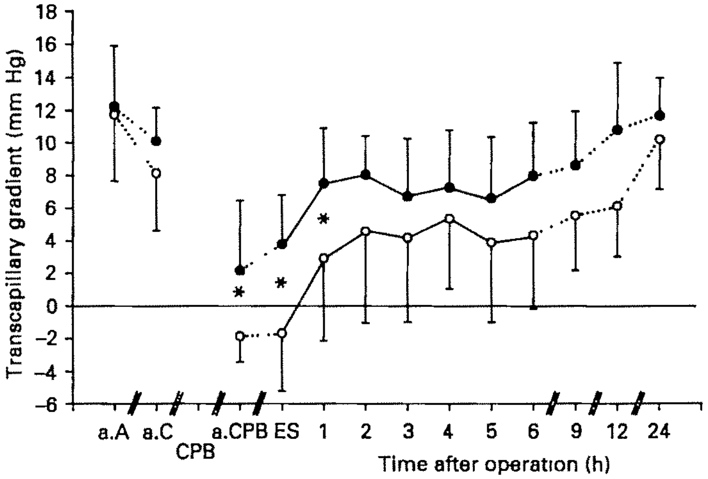

FIG. 3. Time course of the transcapillary gradient (difference between colloid osmotic pressure and pulmonary capillary wedge pressure) in the Ringer's lactate (RL) (○) (*n* = 10) and human albumin (●) (*n* = 10) groups (mean, SD). During cardiopulmonary bypass the transcapillary gradient decreased in both groups, but was always less in the RL group, becoming negative in this group until the end of surgery. $P < 0.05$ for ANOVA overall difference between groups; *$P < 0.05$ for Tukey HSD *post hoc* comparison.

cantly smaller (from 19.3 (2.3) mm Hg to 15.2 (1.1) mm Hg (30 %)) (fig. 2). In the postoperative period, both groups showed a continuous increase in colloid osmotic pressure but the preoperative values were not achieved in the RL group; the difference in colloid osmotic pressure between the groups was present for the next 24 h. The difference between colloid osmotic pressure and pulmonary capillary wedge pressure (COD—PCWP) has been suggested as an index of the transcapillary Starling forces regulating fluid transfer [23]. A marked decrease in this gradient was observed in both groups. The change was more pronounced in the RL group and even decreased below zero in this group immediately after cardiopulmonary bypass (fig. 3). Consequently, a significant increase in extravascular lung water by more than 60 % occurred in the RL

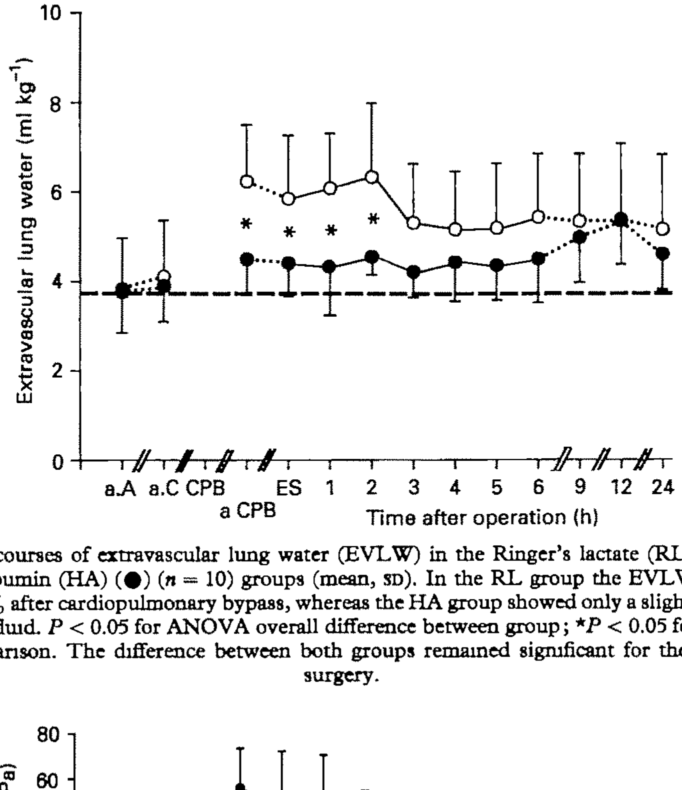

FIG 4. Time courses of extravascular lung water (EVLW) in the Ringer's lactate (RL) (○) ($n = 10$) and human albumin (HA) (●) ($n = 10$) groups (mean, SD). In the RL group the EVLW increased by more than 60 % after cardiopulmonary bypass, whereas the HA group showed only a slight accumulation of pulmonary fluid. $P < 0.05$ for ANOVA overall difference between group; $^*P < 0.05$ for Tukey HSD *post hoc* comparison. The difference between both groups remained significant for the first 2 h after surgery.

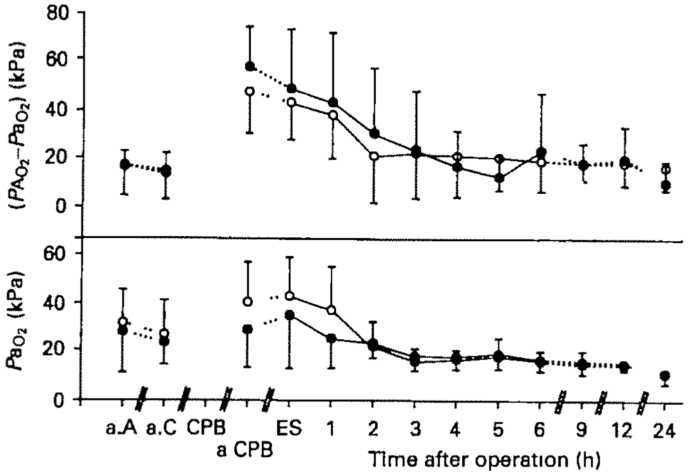

FIG. 5. Time courses of the alveolar–arterial oxygen partial pressure difference ($PA_{O_2} - Pa_{O_2}$) and arterial oxygen partial pressure (Pa_{O_2}) in the Ringer's lactate (○) ($n = 10$) and human albumin (●) ($n = 10$) groups (mean, SD). No statistically significant differences between groups.

group. In contrast, in the HA group, there was only a slight tendency to increased extravascular lung water in the postoperative period (fig. 4). The difference between both groups was significant for the first 2 h after the end of surgery. However, the time courses of arterial oxygen pressure (Pa_{O_2}) and of alveolar–arterial oxygen difference ($PA_{O_2}-Pa_{O_2}$) were the same in both groups (fig. 5), as was the average time to tracheal extubation (table II).

DISCUSSION

The results of the present study demonstrate that addition of albumin in a sufficiently high concentration to the priming solution may prevent accumulation of extravascular lung water after open heart surgery. In the HA group there was only a slight tendency to accumulation of extravascular lung water. Although the calculated albumin content of the priming volume was 4% and therefore considerably greater than that used in all previous investigations [11–15], a slight decrease in colloid osmotic pressure was found in this group. In the RL group, the decrease in colloid osmotic pressure was much more pronounced and was accompanied by a marked increase in extravascular lung water.

Accumulation of extravascular lung water after cardiopulmonary bypass may result from several mechanisms. The contact of blood with the foreign surfaces of the extracorporeal circulation activates several inflammatory mediators. Thromboxane B_2, fibrinopeptide, elastase and complement C3a have been shown to be increased in plasma after cardiopulmonary bypass [3, 8, 9, 24, 25]. Neutrophils are activated by mediation of complement C5a and sequestered into the pulmonary circulation with the onset of partial bypass [3, 8, 24]. In principle, all these factors may cause capillary endothelial damage, but accumulation of extravascular fluid does not necessarily occur. In fact, it has been demonstrated in animal experiments that the lymph drainage of the lung can increase markedly and compensate for capillary leaks to a considerable extent [10].

Furthermore, after cardiopulmonary bypass there is not only increased vulnerability of the endothelial barrier, but the intravascular Starling forces regulating transcapillary fluid exchange (intravascular hydrostatic pressure and colloid osmotic pressure) are altered also in an unfavourable manner. Hydrostatic pressure is often increased by left ventricular dysfunction: the left ventricle is compromised by the surgical procedure and may have postischaemic dysfunction because of unavoidable intraoperative ischaemic episodes such as crossclamping and cardioplegia. A greater preload and sometimes inotropic support by catecholamines is required to meet the demands of the circulation. Arterial pressure within the pulmonary circulation is therefore often increased. Additionally, the vascular resistance of the pulmonary circulation is increased, probably because of formation of thromboxane from platelets [24]. As a result, microvascular hydrostatic pressure is increased and this enhances transendothelial fluid transfer. In addition, haemodilution of the blood by the priming volume of the machine causes a considerable decrease in plasma protein concentration and colloid osmotic pressure; thus, after cardiopulmonary bypass, the additive effect of all these mechanisms may lead to exhaustion of the transport capacity of the pulmonary lymph system and extravascular fluid accumulates.

One of the first investigations on the problem of lung water development after cardiopulmonary bypass was performed by Byrick, Colin and Noble [11]. They compared the effects of two types of priming solutions on the postoperative development of extravascular lung water. The machine was primed with either two units of plasma with lactated Ringer's solution or with lactated Ringer's solution alone. In this study, the greatest protein concentration in the prime volume was only 1.2%—far below the physiological range. Thus it is not surprising that no major differences in the time course of changes in colloid osmotic pressure were observed between the two groups. Only a slight increase in extravascular lung water was observed at the end of surgery. In contrast to many other studies, accumulation of extravascular lung water was observed during the first and second days after operation. This finding differs from those of other investigations [12, 13] and of the present study, in which accumulation of extravascular lung water occurred only during the first 4 h after operation. In contrast with most other investigations [1, 2, 12, 13, 15], in Byrick's study [11] colloid osmotic pressure did not reach preoperative values during the first day after operation. Although the immediate postoperative increase of COP to 70–80% of preoperative values is similar to that in other investigations, the COP in Byrick's study remained at these values for the next 2 days. This suggests postoperative fluid management with larger amounts of crystalloids and this may explain the increased extravascular lung water on the first and second days after operation.

In principle, results similar to the present investigation have been described by Boldt and colleagues [16], who found a significant increase in post-bypass lung water in those patients who received preoperative haemodilution with Ringer lactate and underwent extracorporeal circulation with a priming volume of 2000 ml of pure crystalloid. A two-stage cannulation technique was used; ligation of the venae cavae was not performed and the total volume of cardioplegic solution entered the systemic circulation via the coronary sinus. The additive effects of preoperative haemodilution, pure crystalloid priming and cardioplegic solution resulted in an extreme decrease of systemic colloid osmotic pressure (to less than 6 mm Hg on average). Consequently, lung water increased significantly immediately after the end of bypass and was even greater 45 min later.

Interestingly, in the study of Boldt and colleagues [16], the control group (with no significant evidence of lung water accumulation) was comparable to the RL group of the present investigation, which had significant accumulation of lung water. In fact, the time courses of colloid osmotic pressures match very well and are in agreement with many other studies in which pure crystalloid solutions were used for cardiopulmonary bypass [2, 11–15]. However, there were some differences. Boldt observed only a slight, insignificant increase in lung water after surgery; furthermore, under control conditions (before surgery) an extravascular lung water of nearly 6 ml kg^{-1} was found, which is considerably more than in the present study.

These differences result probably from methodological differences; it is known that the conventional technique of lung water measurement with only a single measuring site, blood withdrawal for tracer detection and monoexponential extrapolation of the tracer curves, leads to a systematic error with overestimation of extravascular lung water [18, 26–28]. Two sources of error are mainly responsible for this overestimation: prepulmonary heat exchange with extravascular tissues, and contamination of the aortic temperature curve by recirculation leading to incorrect estimation of mean temperature transit times [18]. The distribution volume for prepulmonary heat exchange is included erroneously in extravascular lung water measurements assessed by the conventional method and therefore results in an additive error. A systematic additive error might also impair the sensitivity of the measuring method, as minor absolute changes in lung water might be relatively small in comparison with baseline measurements. This might explain why Boldt and colleagues, with high control values for extravascular lung water, observed only a slight insignificant increase in lung water after extracorporeal circulation. In the present study, prepulmonary heat exchange was visible by means of a time delay between the temperature and the dye curve in the pulmonary artery. This slight time delay between both pulmonary tracer curves was observed consistently in all measurements of this study.

In the present investigation a deconvolution technique with two sites of tracer measurement (pulmonary artery and descending aorta) was used. By this method, tracer mean transit times can be calculated on the basis of the respective transpulmonary transport functions. In principle, the additional information, which is supplied by the pulmonary artery catheter, is used to eliminate the pattern of the tracer bolus at the entrance to the organ and to compute the tracer curve at the output from the organ, which would result from an ideal impulse input into the pulmonary artery. The deconvolution approach is, therefore, independent of the shape of the input signal. Differences in shape of the pulmonary curves and recirculation of the tracer do not therefore affect the resulting transport functions. Thus the average control value for extravascular lung water in this study (3.8 ml/kg body weight) was considerably lower than the majority of control values reported in the literature. An important effect of avoiding systematic additive errors is increased sensitivity to small changes in lung water.

Although a considerable postoperative increase in lung water occurred in patients without colloid osmotic priming, the clinical significance of this finding remains unclear. Because of expense, it is questionable if an albumin priming should be advocated for all patients. No differences were observed in postoperative pulmonary function between the two groups, indicating that factors other than changes in extravascular lung water may be more important for postoperative recovery of respiratory function. Probably, excessive haemodilution has to occur before the resulting lung water accumulation leads to fatal pulmonary dysfunction. We suggest that a priming volume with a high colloid osmotic pressure should probably be used only in those patients who have additional risk factors for postoperative pulmonary dysfunction.

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SENSORY INFORMATION PROCESSING DURING GENERAL ANAESTHESIA: EFFECT OF ISOFLURANE ON AUDITORY EVOKED NEURONAL OSCILLATIONS

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SUMMARY

There is evidence from neuropsychological and psychophysical measurements that sensory information is processed in discrete time segments. The segmentation process may be described as neuronal oscillation at a frequency of 30–40 Hz. Stimulus-induced neuronal oscillations of this frequency are found in the middle latency range of the auditory evoked potential (AEP). We have studied the effect of different end-tidal concentrations of isoflurane on auditory evoked 30–40 Hz neuronal oscillations. We studied 13 patients undergoing intra-abdominal urological and gynaecological procedures. AEP were recorded in the awake state and during end-expiratory steady state isoflurane concentrations of 0.3, 0.6 and 1.2 vol%. These incremental doses of isoflurane caused a stepwise decrease in frequency of oscillations. The decrease in oscillation frequency and sometimes the disappearance of oscillatory components may be interpreted as suppression of sensory information processing. The measurement of auditory evoked neuronal oscillations in the AEP appears to be a promising tool to monitor both sensory information processing capacity and depth of anaesthesia.

KEY WORDS

Anaesthesia· general Anaesthetics, volatile isoflurane Brain auditory evoked potentials.

The aim of general anaesthesia is to suppress consciousness during surgery. However, it is not clear what mechanisms are responsible for conscious awareness, although several theories have been proposed [1–4]. Sensory information is processed in spatially separate areas within the brain. This concept of segregation of function is particularly well established for vision [5, 6]. Spatial segregation of function has an apparent parallel in the time domain, because it is suggested by several studies that information processing is not continuous in time and sensory input is processed in discrete successive steps.

If the temporal order threshold is determined for visual, auditory and tactile stimuli, similar values are obtained for each modality (20–30 ms [7, 8]). It is interesting to note that these three modalities show almost identical order thresholds, although fusion thresholds for stimuli are very different [9]. Further examples of discontinuous processing of sensory information come from histograms of choice reaction time and latencies of saccadic and pursuit eye movements. Such histograms are often multimodal with intermodal distances of 30–40 ms [10–13]. The multimodalities may be interpreted as an expression of preferred time zones set up by neuronal relaxation oscillations [12], within which reactions are located—that is, temporally segregated. In accordance with these psychophysical and neuropsychological findings, extra- and intracellular recordings in neurones demonstrate the existence of a 40-Hz oscillatory activity in the brain [14–16], which can be observed also in the spontaneous electroencephalogram (EEG) [17–19] and in sensory evoked potentials of different modalities [20–23].

The dominance of the 40-Hz oscillation is represented prominently in the midlatency response of auditory evoked potentials [20, 24]. We

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have found suppression of the 40-Hz oscillatory component after induction of anaesthesia with etomidate [24]. These results indicate a potential link between the oscillatory components in the auditory evoked potential as an expression of information processing and the functional state of the brain. The aim of this study was to evaluate qualitative and dose-dependent effects of the volatile anaesthetic isoflurane on neuronal oscillations monitored in the midlatency range of auditory evoked potentials (AEP).

PATIENTS AND METHODS

Patients and anaesthesia

Following institutional Ethics Committee approval and informed consent, we studied 13 patients (aged 28–65 yr, ASA class II) undergoing intra-abdominal urological or gynaecological procedures. None of the patients had either otolaryngological or neurological disorders or was receiving any medication. Patients were premedicated orally with flunitrazepam 2 mg, 45–60 min before the beginning of the study. To eliminate nociceptive stimuli during the operative procedure, continuous lumbar extradural analgesia (EA) was administered using 0.5% bupivacaine. The level and effectiveness of EA was tested by pinprick. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} was given to produce muscular relaxation. After tracheal intubation, the patient's lungs were ventilated with 50% oxygen and isoflurane in air to maintain normocapnia. The end-expiratory concentration of isoflurane was monitored continuously with a multigas analyser (Siemens). AEP were measured after 15 min steady state concentrations of isoflurane 1.2, 0.6 and 0.3 vol% after a minimum time interval of 45 min after anaesthetic induction. Systemic arterial pressure was monitored invasively, and mean arterial pressure was maintained greater than 80 mm Hg. Core temperature was measured with an oesophageal probe and maintained greater than 34.5 °C using heated blankets and infusion of warmed solutions.

Recording of auditory evoked potentials

The electrodiagnostic system Pathfinder I (Nicolet Instr.) was used for acoustic stimulation, registration and analysis of evoked potentials. Rarefaction clicks of 0.1 ms and 70 dB above the normal hearing level were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39). For recording, silver–silver chloride electrodes were positioned at Cz and A_1 with Fpz as ground (according to the international 10–20 system). The impedance of all electrodes was kept less than 0.5 kΩ. An epoch of 100 ms (bin width 0.2 ms) was bandpass filtered (1–1500 Hz) with an analog Butterworth-filter (roll-off 6 dB $octave^{-1}$) and averaged across 1000 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artefact detector rejected signals greater than 96% of full scale. To guarantee reliability of the signal and correct transmission and transduction of the acoustic stimuli, evoked potentials without a brainstem response (peak V) were rejected also. AEP were measured in the awake patient and then at steady state end-expiratory concentrations. One AEP represents the averaged activity during approximately 1 min.

Analysis of auditory evoked potentials

For each situation, we analysed the AEP of individual patients and an interindividual grand average (GA), calculated from the AEP of all 13 patients. Off-line data analysis was as follows: latencies of the peaks V, Na, and Pa and relative amplitudes from peak Na to peak Pa were measured. Latencies of all peaks were compared with the Wilcoxon test (two-tailed, minimum level of significance 5%, including Bonferroni's correction). For frequency analysis of the potential, in addition to the classical Fast Fourier Transformation (FFT), a rank-correlation procedure (RCF) was used. In contrast to other frequency analysing methods, the rank-correlation method provides also a high frequency resolution for short epoch signals such as the AEP. The method is based on a non-parametric procedure for the detection of oscillations in time series [25, 26] and has been used successfully in another study [27] to determine main oscillation frequencies perioperatively by recorded AEP. The RCF was calculated for a time window of approximately 80 ms, always beginning with peak Na.

RESULTS

Auditory evoked potentials were recorded successfully in each patient. Figure 1 shows a rep-

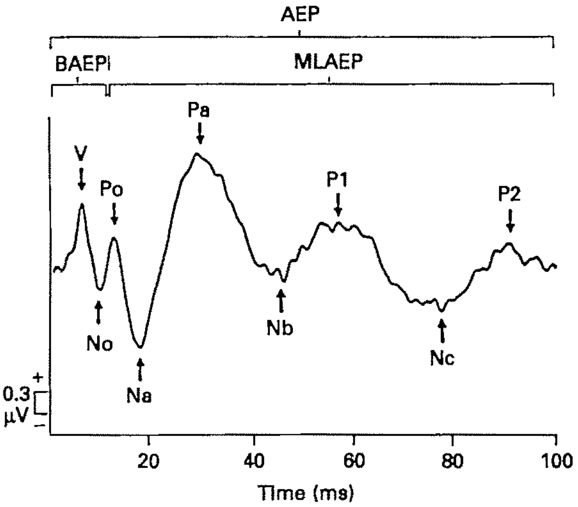

FIG. 1. Auditory evoked potential (AEP) of an awake patient. BAEP = Brainstem-generated auditory evoked potential; MLAEP = midlatency auditory evoked potential. Arrows indicate peaks.

resentative AEP of a premedicated, awake patient immediately before induction of anaesthesia. It consists of two distinct components: a brainstem-generated AEP (BAEP) and a midlatency AEP (MLAEP). For the BAEP, a prominent peak with a latency of 5.8–6.2 ms (corresponding to the brainstem potential V of Jewett's nomenclature) was found in each patient. This robust short-latency, brainstem-generated component served as a reference for a correct and successful transduction and transmission of the auditory stimulation. The brainstem potential was followed by the so-called No/Po complex in a latency range between 10 and 15 ms after stimulation. The No/Po potentials were contaminated occasionally with sonomotor potentials in the awake patients.

In the MLAEP, beginning 15–20 ms after stimulus application, a sequence of negative and positive peaks depicts a stimulus-dependent, oscillatory process. The peaks Na and Pa were identified easily in all cases. The following components, termed Nb, P1, N1 and P2 were detectable only in the awake state or during low concentrations of isoflurane.

AEP and corresponding power spectra (Fast Fourier Transformation) of the midlatency oscillations for a characteristic single patient in the awake state and during the three different isoflurane concentrations are shown in figure 2. Midlatency components beginning with peak Na and Pa were obviously reduced in amplitude and prolonged in latency with increasing doses of isoflurane, whereas the amplitude and configuration of brainstem potential V did not change with the level of anaesthesia. The FFT assigns a dominant frequency of 40 Hz to the midlatency oscillation of the evoked potential. Under general anaesthesia using 0.3% isoflurane, the observable increase in peak latencies resulted in a decrease in the leading

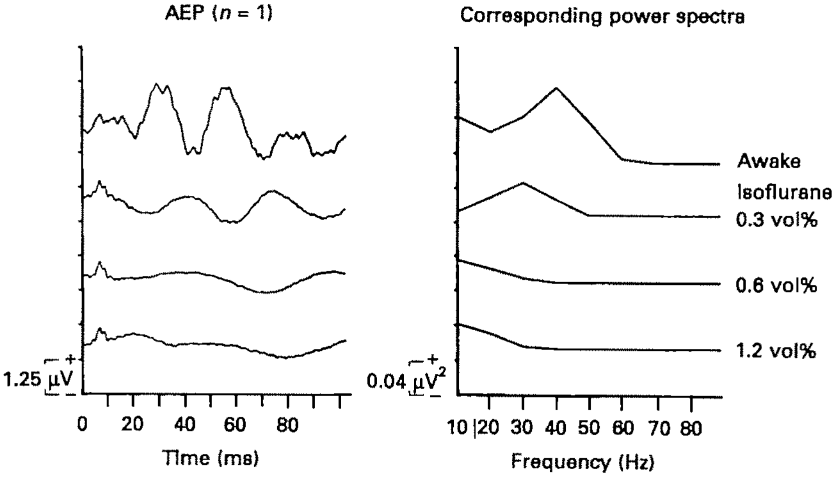

FIG. 2. Auditory evoked potentials (AEP) and corresponding power spectra from a single patient. The graph shows data from the awake state before induction of anaesthesia and during different concentrations of isoflurane. Note the slowing down and disappearance of the oscillatory component from the midlatency range and stability of the brainstem evoked potentials under anaesthesia, the latter indicating intact sensory transduction mechanisms.

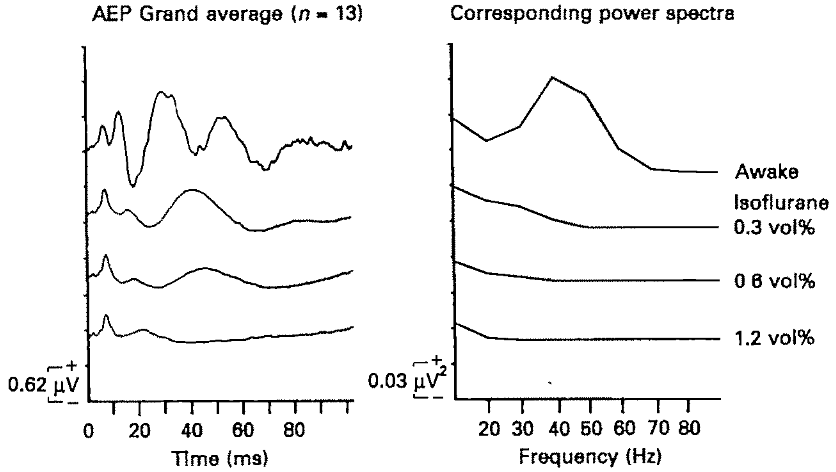

FIG. 3. Grand averages of auditory evoked potentials (AEP) and their power spectra from 13 patients. Data are shown from the awake state before induction of anaesthesia and for different concentrations of isoflurane.

oscillation frequency to 30 Hz. This oscillation frequency of the MLAEP decreased again with 0.6% isoflurane to an oscillation of 10 Hz and remained constant with 1.2% isoflurane.

Figure 3 shows the interindividual grand averages of AEP recorded from all 13 patients. The results of the grand averages confirm the suppression of amplitude and reduction of oscillation frequency seen in the single patient. Oscillation frequency again decreased in a stepwise manner. The first suppression in oscillation frequency was associated with isoflurane concentrations of 0.3%. Isoflurane concentrations of 0.6 vol% caused a further reduction of midlatency oscillations, whereas 1.2% isoflurane resulted in their complete abolition.

Mean values and SEM for the latencies of the peaks V, Na and Pa, and Na/Pa amplitudes are presented in figure 4. The latencies of the peaks V, Na and Pa had a low interindividual variability. A graded and statistically significant ($P < 0.05$) increase with isoflurane concentration was observed

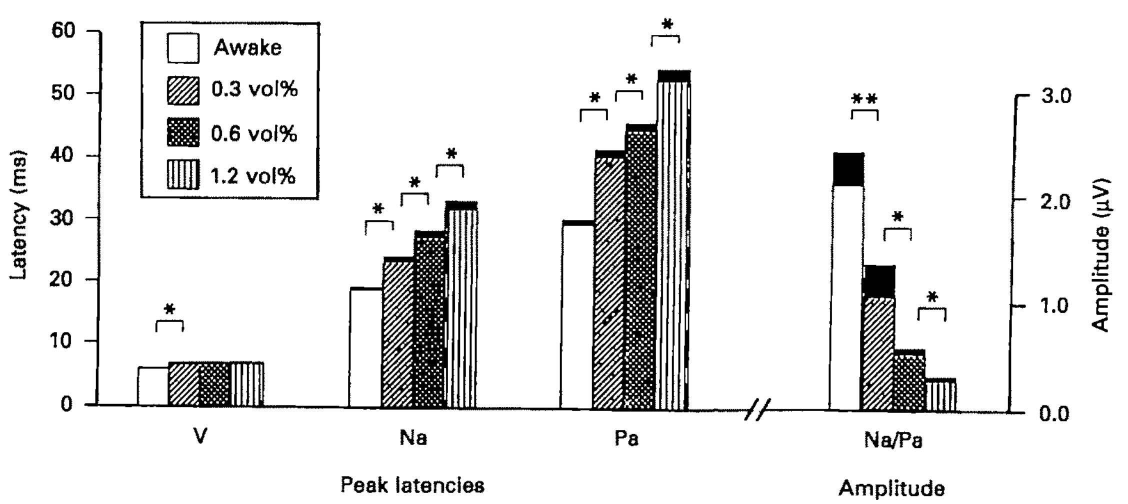

FIG. 4. Means and SEM (■) of peak latencies V, Na, Pa (left side) and Na/Pa amplitudes (right side). *Significant differences between experimental conditions tested with the Wilcoxon test for matched samples: $*P \leqslant 0.05$; $**P \leqslant 0.01$.

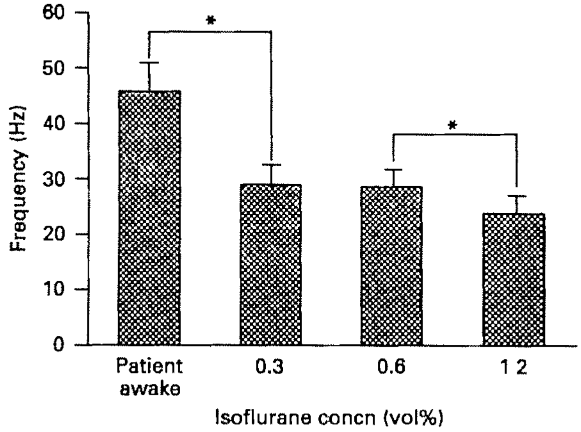

FIG. 5. Means, SEM of oscillation frequency measured with the rank-correlation function for each experimental situation. Significant difference between conditions: $*P < 0.05$ (Wilcoxon test for matched samples).

for both Na and Pa latencies. A significant ($P < 0.05$) increase in the short latency brainstem potentials (peak V) was detectable only between the awake state and the 0.3% isoflurane. A further graded change in latency for this component under increasing concentrations of isoflurane was not seen. The Na/Pa amplitudes were significantly ($P < 0.05$) reduced.

Figure 5 shows the means and SEM of the dominant oscillation frequency for all 13 patients according to the concentration of isoflurane. Mean oscillation frequency ($P < 0.05$) decreased significantly from about 45 Hz in the awake state to 29 Hz with 0.3% isoflurane. A further increase of isoflurane concentration to 0.6% resulted in a small and insignificant shift to 28 Hz. With 1.2% isoflurane, oscillation frequency of the MLAEP decreased significantly ($P < 0.05$), to 23 Hz.

DISCUSSION

In all patients, an oscillation frequency of approximately 40 Hz was observed in the awake state. This finding confirms the existence of a stimulus-dependent and interindividual constant oscillatory brain mechanism for sensory information processing. It is not clear if these oscillations are caused by a single generator or by a suprasegmental chain of generators. Studies have suggested, however, that oscillations of the MLAEP represent the activation of several generators situated at different brain levels [1].

Isoflurane is a non-specific acting general anaesthetic agent and induces a dose-dependent suppression of auditory evoked neuronal oscillations. The suppression of neuronal oscillations was reflected by prolongation of latencies and reduction of amplitudes of the MLAEP components, mainly the peaks Na and Pa. The observed influence of volatile anaesthetic agents on latencies and amplitudes of the MLAEP has been demonstrated previously [28–30]. Changes in these parameters have been proposed, therefore, as an objective criterion for depth of anaesthesia. Our results suggest that direct measurement of neuronal oscillations by frequency analysis seems preferable, for the following reasons.

Latencies and amplitudes of MLAEP components are connected only indirectly to these oscillations. Peaks Na and Pa, for instance, are prolonged in latency with each increment of isoflurane concentration. This does not necessarily represent disturbed sensory information processing. Prolongation of midlatency peaks might also be caused by slowed transmission of the acoustic stimulus from the receptor to the primary auditory cortex. Although Na and Pa latencies gradually increased from the awake state to 1.2% isoflurane, the difference in Na–Pa latency for 0.3 and 0.6% was the same, indicating a change in phase but not in frequency of the neuronal oscillation. This observation was confirmed by frequency analysis, which showed that neuronal oscillations were reduced significantly for 0.3 and 1.2% isoflurane only. The fact that oscillation frequency did not change with increasing concentrations from 0.3 to 0.6% isoflurane indicates that these doses did not suppress significantly those structures involved in the oscillatory process. As oscillation frequency of the MLAEP depends mainly on the Na/Pa complex, it could be expected that the underlying generators of these midlatency peaks are unaffected with concentrations of isoflurane less than or equal to 0.6%. It has been proposed recently [31, 32] that the Na/Pa complex is generated in the primary auditory cortex of the temporal lobe. Therefore, despite prolonged peak latencies, it can be assumed that concentrations less than or equal to 0.6% do not suppress sensory information processing of acoustic stimuli at the level of the primary auditory cortex.

Amplitudes are reduced gradually by isoflurane also, but have a greater interindividual variability compared with latency and oscillation measures.

This makes it difficult to evaluate adequate anaesthesia with this parameter. The only way to use amplitudes as an indicator of anaesthetic depth would be to compare pre- and intraoperative amplitudes individually. Nevertheless, amplitudes are very sensitive to biological and technical influences. Interindividual variability is caused by subjective hearing level, mass of the generator and distance between generator and electrode. Moreover, intraindividual changes might occur especially during operative procedures such as extracorporal circulation in cardiac surgery. In these situations, alterations of skin resistance caused by sweating or reduced skin perfusion are quite common. A suppression of amplitudes, therefore, seems only a vague predictor of the functional state of the brain.

In addition to these practical implications, there are theoretical reasons for preferring measurement of neuronal oscillations as an indicator of the state of the brain under anaesthesia. The proposed neuropsychological model underlying sensory information processing is based on the existence of a time segmentation process. This process synchronizes sensory information from different modalities and by doing so allows the organism to identify sensory events in a time ordered structure [3, 33]. The clinical observation that patients often report no lapse of time during anaesthesia is relevant in this context [24]. It can be speculated that the suppression of the neuronal oscillations results in a disturbance of time perception or even in a subjective "loss" of time. This impression is different from the evaluation of time after natural sleep, which may be quite accurate [34]. In agreement with this observation, auditory evoked 40-Hz responses could be recorded during most phases of night sleep [35].

According to the underlying model of sensory information processing and temporal organization of perception [3, 36, 37], not only time perception but also consciousness in general should be interrupted when the oscillating activity is suppressed. One way of testing this hypothesis is to gain insight into the physiological mechanism of the proposed neuronal oscillations using pharmacological intervention. The anatomical localization of the neuronal oscillation generator has not yet been identified, but it is proposed that one or more generators localized in the midbrain and cortical structures produce the 40-Hz response in the EEG and sensory evoked potentials of different modalities [1].

General anaesthetic agents seem to be a useful tool to test the neuropsychological hypotheses of consciousness. With the presented neuropsychological model, suppression of the neuronal oscillations should allow the stimulus to enter the brainstem, but any higher cognitive function, such as perception or even retention in memory, should be blocked. The latter has yet to be tested. In this context, it would be of interest to investigate the behaviour of the neuronal oscillator under anaesthetic agents with psychomimetic effects such as ketamine or during anaesthetic regimens associated with intraoperative awareness such as high-dose fentanyl anaesthesia [38].

In the present study, AEP with 0.6% isoflurane still exhibited midlatency oscillations of about 30 Hz, despite prolonged latencies. This corresponds well with clinical observations of inadequate anaesthesia under these concentrations. Therefore, to guarantee suppression of consciousness and sufficient "depth of anaesthesia", isoflurane should be used only in concentrations exceeding 0.6%.

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BARBITURATE ALTERATION OF RESPIRATORY RHYTHM AND DRIVE IN ISOLATED BRAINSTEM–SPINAL CORD OF NEWBORN RAT: STUDIES AT NORMAL AND HYPERBARIC PRESSURE

A. TARASIUK, Y. GROSSMAN AND J. J. KENDIG

SUMMARY

High pressure and anaesthetic agents are mutual antagonists in intact animals, but antagonism is not observed in isolated nerve cells. In order to test the hypothesis that a neural network might display pressure–anaesthetic antagonism not found in simpler systems, we have examined the effects of pentobarbitone at normal pressure and at 10.1 MPa helium pressure on the rhythmic activity of medullary respiratory centres of isolated brainstem and spinal cord from 0–3 day old rats. Pentobarbitone 5–80 μmol litre^{-1} *depressed the frequency, amplitude and area of spontaneous bursts recorded from* C_5*, reduced respiratory drive, and altered the response to trigeminal nerve root stimulation. Compression to 10.1 MPa decreased ventilatory frequency and respiratory drive, and either did not interact with or enhanced the depressant effects of pentobarbitone. Pentobarbitone and helium pressure altered the response to trigeminal nerve root stimulation in the same manner. The results are consistent with additive rather than antagonistic effects of pressure and a barbiturate on the determinants of output from the respiratory centre–motor neurone pathway. Pressure–anaesthetic antagonism may be a property unique to the neural circuitry which underlies awake behaviour and pressure-induced seizures, rather than reflecting a fundamental molecular-level antagonism.*

KEY WORDS

Anaesthesia · barbiturates Hyperbaria · HPNS, pressure reversal Theories of anaesthetic action pressure reversal.

The interactions between anaesthetics and hyperbaric pressure are of interest because of their mutual antagonism: high pressure increases anaesthetic requirement (pressure "reversal" of anaesthesia) [1], and anaesthetics inhibit some components of the high pressure nervous syndrome, a group of symptoms including tremor and seizures. Previous studies have examined interactions between anaesthetics and pressure on evoked activity in isolated nerve and nerve–muscle preparations [2–9]. The results have revealed several instances in which anaesthetics and pressure act in the same direction, particularly at excitatory synapses. The spontaneous rhythmic activity generated by the respiratory centres in the medulla is a more complex neural behaviour, relevant both to the fundamental effects of pressure and anaesthetics on neuronal processes, and to their effects on the intact organism. Furthermore, it offers the advantage of normal activity patterns among the interacting neurones, rather than the unphysiological frequency and synchronicity characteristic of external artificial stimulation. It is of interest, therefore, to see if there may be an unexpected interaction between anaesthetics and pressure on a network of interacting neurones that would not be predicted from results on simpler systems.

Because of its narrow cross-section and relatively low oxygen requirements, the isolated brain

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stem and spinal cord of newborn rats may be maintained *in vitro* for several hours [10]. In addition to reflex responses to stimulation of sensory roots, the preparation generates spontaneous rhythmic bursts of motor neurone activity in ventral spinal roots C_1 and C_5; this pattern has been identified with ventilatory output [11–13]. Unlike various slice preparations, normal pathways and connections are preserved, while the isolated preparation is more accessible to experimental control and manipulation than are the respiratory centres *in vivo*. We have reported previously the effects of pressure alone on the ventilatory rhythm of the isolated brainstem–spinal cord [14]: pressure (10.1 MPa) decreased the frequency of spontaneous ventilatory rhythm, reduced respiratory drive, and altered the influence of trigeminal nerve root stimulation from inhibitory to excitatory. The present study has examined interactions between hyperbaric pressure and anaesthetic agents.

METHODS AND MATERIALS

Rats 0–3 days old were anaesthetized with diethyl ether until loss of response to tail pinch was observed. The animals were decerebrated under anaesthesia by an oblique section through the cranium which severed the brain at the mid-collicular level. The remaining portion of the skull and attached vertebral column were removed to a dish containing chilled oxygenated cerebrospinal fluid. After the dorsal bony covering and cerebellum were removed, the portion of the central nervous system from the posterior collicular level of the brain through the mid-thoracic level of the spinal cord was gently dissected free, with care taken to preserve cranial and cervical nerve roots [12], and mounted in a superfusion chamber contained within the pressure chamber. The preparation was superfused constantly with oxygenated (95% oxygen–5% carbon dioxide) bicarbonate-buffered Ringer's solution of composition (mmol litre^{-1}): NaCl 123, KCl 5, NaH_2PO_4 1.2, $CaCl_2$ 2.0, $MgSO_4$ 1.3, $NaHCO_3$ 26, glucose 30, at pH 7.3 and temperature 27 °C. The solution was equilibrated with the gas mixture outside the chamber and delivered to the bath by a high pressure pump at an exchange rate of 15–20 bath volumes min^{-1}. Suction recording electrodes were placed on the cut ends of ventral spinal root C_5, which gives rise to the phrenic nerve, and C_1, which innervates some of the accessory muscles of ventilation. A very high proportion of motor neurones in these roots innervate the muscles of ventilation, and rhythmic activity recorded from them reflects ventilatory outflow [13]. Suction stimulating electrodes were placed on cranial nerve root V (trigeminal).

Spontaneous bursts of motor neurone activity were recorded from ventral roots C_1 and C_5, and their frequency was determined. The area under the curve of a single ventilatory burst was plotted and measured by "Morphometer" software (Woods Hole Educational Association, Inc). Respiratory drive was defined as frequency of the spontaneous rhythmic activity multiplied by the mean area of the ventilatory burst. Delay between C_1 and C_5 was measured as the time between beginning of the ventilatory bursts measured at the respective roots. In some experiments, trigeminal nerve stimulation, which inhibits respiratory drive, was used to examine differences between spontaneous ventilatory activity and activity modulated by sensory input.

Initial experiments showed that applications of pentobarbitone in the superfusate at concentrations up to 10 µmol litre^{-1} over the time required to achieve a steady state effect produced reversible depression of ventilatory rhythm. Prolonged application of higher concentrations produced irreversible depression. Equilibrium or steady state responses to pentobarbitone were obtained therefore by exposure to a single concentration of 5–8 µmol litre^{-1} for 20–25 min. In order to examine the effect of pressure on the pentobarbitone dose–response relationship, dose–response curves for the effect of the drug on spontaneous frequency were constructed from brief (45–100 s) exposures, from which the preparation recovered fully. Frequency was measured over the last 25–30 s of exposure to pentobarbitone and compared with the frequency measured during the immediately preceding 2–3 min control interval.

Pressure was applied by admitting helium to the chamber to a pressure of 10.1 MPa. Measurements at pressure were made 20–25 min after the compression step. In the first part of the study, a dose–response curve to brief application of pentobarbitone was constructed at normobaric pressure, followed by washout and recovery. The pressure was then increased to 10.1 MPa, and the dose–response curve repeated (figs 1, 2). In the second part, duplicate estimates of ventilatory responses were obtained in control conditions and following application of pentobarbitone

5–8 µmol litre^{-1} to steady state; the preparation was compressed, and duplicate measurements obtained at pressure in the presence of the drug (figs 3–5). Decompression measurements were attempted, but seldom successful.

In an experiment involving respiratory control, it is important to consider possible effects of the experimental conditions on oxygen and carbon dioxide tensions and on pH. Recorded activity monitored in the sealed pressure chamber at normal pressure resembled that reported in the literature [10–12] and remained stable for several hours. Helium pressure might exert several effects: physiological effects of helium itself, and pressure-associated changes in buffer ionization and gases in solution. The effects of helium in many studies appear to be primarily those of pressure, corrected by a small amount for the limited lipid solubility of this inert gas [1]. Bicarbonate buffer dissociation constants are pressure-sensitive, but 10.1 MPa would result in a change in pH of less than 0.05 [15]. As the perfusate is equilibrated at normal pressure and flows rapidly past the tissue, oxygen and carbon dioxide in solution around the preparation are independent of their partial pressures in the chamber. Their equilibrium pressures would be expected to increase by approximately 14% as a result of hydrostatic pressure at 10.1 MPa [16].

Dose–response data for pentobarbitone at normobaric and hyperbaric pressure were analysed by ANOVA. Linear regression analysis was used to compare the slope of the pentobarbitone dose–response curve at normal and hyperbaric pressure. Steady state effects of pentobarbitone at 0.1 and 10.1 MPa were measured as change from the 0.1 MPa control, and compared by paired *t* test.

RESULTS

Properties of the isolated brain stem–spinal cord

The isolated medulla–spinal cord generates a spontaneous rhythmic discharge in motor neurones of the ventral roots which innervate the muscles of ventilation (fig. 1). The rhythmic bursts, which are identified as output from ventilatory motor neurones, normally remain stable for several hours in the superfused preparation [12]. In a series of 15 preparations, the frequency of the ventilatory burst at 27 °C and 0.1 MPa averaged 7.5 (SD 0.4) bursts min^{-1} in records from C_5; peak amplitudes recorded from C_5 averaged 190 (20) µV; mean duration was 173 (14) ms. In a series of 12 preparations, latency between C_1 and C_5, which may govern co-ordination between the diaphragm and the accessory muscles of ventilation, averaged 78.2 (11) ms. Calculating the respiratory drive as a product of burst area and frequency (Methods) yields a dimensionless number which, under normal experimental conditions, averaged 120 (31) in recordings from C_5 ($n = 10$). Stimulation of the V (trigeminal) cranial nerve in the isolated preparation at normal pressure depressed the frequency of the ventilatory rhythm to an extent governed by the stimulus frequency. This effect of trigeminal nerve stimulation may be related to the reduction in ventilatory drive produced by various types of facial stimulation, and may represent a component of the diving reflex [17–19].

Effects of pentobarbitone on spontaneous rhythmicity

A previous study [14] reported that pressure reduced the frequency of the ventilatory rhythm. Brief applications of pentobarbitone at normo-

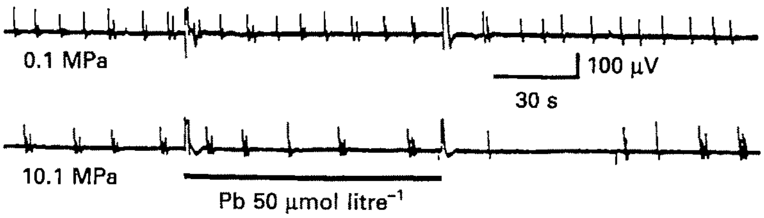

FIG. 1. Records of spontaneous rhythmic bursts of motor neurone discharges in the C_5 ventral root at normal (0.1 MPa) and high (10.1 MPa) pressure. The brainstem–spinal cord was superfused with a solution containing pentobarbitone for (Pb) 50 µmol litre^{-1} for 90 s. Pentobarbitone reversibly depressed spontaneous frequency. Compression to 10.1 MPa had the same effect and enhanced the depressant effect of pentobarbitone. Large deflections at the beginning and end of drug administration are mechanical transients caused by changing solutions at the pump intake.

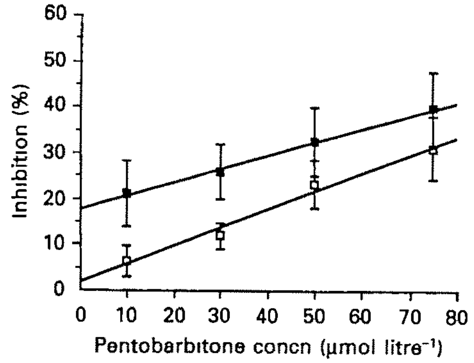

FIG. 2. Effect of brief applications of pentobarbitone on spontaneous ventilatory rhythm frequency at normal (☐ = 0.1 MPa) and high (■ = 10.1 MPa) pressure (mean, SEM). Each of seven preparations was exposed at 0.1 MPa to four concentrations of pentobarbitone and allowed to recover between exposures. The same preparations were compressed to 10.1 MPa and administration of pentobarbitone repeated at that pressure. Frequency was measured as bursts min^{-1}; drug effect was expressed as % inhibition of the control drug-free frequency at 0.1 MPa. There is a significant ($P < 0.001$) concentration–effect relationship ($r = 0.99$ at 0.1 MPa and 0.96 at 10.1 MPa). At pressure the regression of response on pentobarbitone concentration was shifted in the direction of greater effect ($P < 0.01$) with no significant change in the slope.

baric pressure also rapidly and reversibly depressed the frequency of the rhythm throughout the exposure to pentobarbitone (fig. 1) in a dose-dependent fashion (fig. 2). At the steady state concentration of pentobarbitone 5–8 µmol litre^{-1}, there was a small reduction in amplitude of individual bursts (fig. 3) and significant ($P < 0.001$) reductions in duration and in area. Respiratory drive was significantly ($P < 0.01$) reduced as a consequence (fig. 3). There were no effects of pentobarbitone on the latency between bursts recorded in C_1 and C_5.

Effects of pressure on the actions of pentobarbitone

Pressure appeared to increase the sensitivity of the preparation to most of the effects of pentobarbitone. At 10.1 MPa, the effect of brief pentobarbitone applications was enhanced; the dose–response curve was shifted in the direction of greater inhibition of frequency without a change in slope (fig. 2).

Compression to 10.1 MPa in the presence of pentobarbitone produced additional reductions in frequency, area and drive (fig. 3). Duration of individual bursts was not changed further on

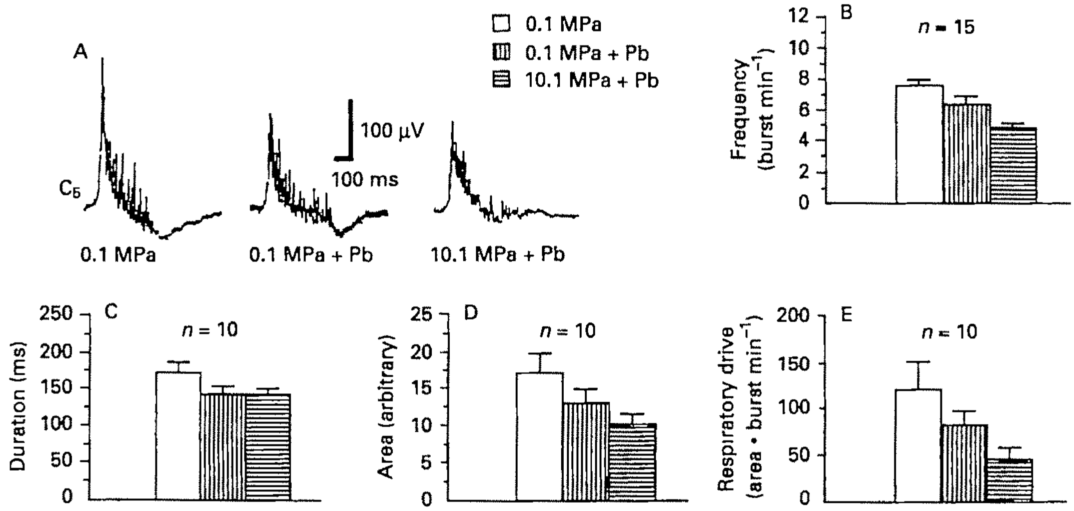

FIG. 3. Effect of prolonged application (to steady state) of pentobarbitone 5-8 µmol litre^{-1} at 0.1 and 10.1 MPa (mean, SEM for n indicated). A: The structure of individual bursts of motor neurone activity shows the effect of pentobarbitone on amplitude and duration at 0.1 MPa and following compression to 10.1 MPa. B: Frequency of the bursts is depressed by pentobarbitone ($P < 0.01$) and depressed further by pressure ($P < 0.01$). C: the duration of the burst was decreased by pentobarbitone ($P < 0.001$); pressure had no further effect on this variable. D: the area of the individual burst was decreased by pentobarbitone ($P < 0.001$); high pressure had a significant additional effect ($P < 0.01$). E: respiratory drive calculated as the product of area and frequency was depressed by pentobarbitone ($P < 0.01$) and pressure had a significant additional depressant effect ($P < 0.05$).

compression. Thus the spontaneous ventilatory activity of the isolated cord revealed either no interaction or additive depressant interactions between a barbiturate anaesthetic and pressure. There was no evidence of antagonism.

Stimulus-modulated ventilatory rhythm

When the effects of pentobarbitone and pressure on the stimulus-modulated ventilatory rhythm were examined, again no antagonistic effects appeared. Normally, stimulation of the V (trigeminal) cranial nerve root depresses the frequency of spontaneous bursts recorded from ventral roots C_1 and C_5 over the entire range of stimulus frequencies. Application of pentobarbitone 5–8 μmol litre^{-1} altered the shape of the stimulus–response curve. At low stimulus frequencies (0.1–0.2 Hz), trigeminal nerve stimulation of the pentobarbitone-treated preparation increased rather than decreased burst frequency (fig. 4). At greater stimulus frequencies (0.5–1 Hz), pentobarbitone had no effect (fig. 4). Compression to 10.1 MPa in the presence of the drug had no effect over the entire range of stimulus frequencies (fig. 5).

The above effects of trigeminal nerve stimulation were observed during prolonged (1-min) stimulus trains at low frequency (0.1–1 Hz). Brief (10-s) stimulus trains at greater frequency (10 Hz) were also used. Under normobaric conditions, such stimulation of the trigeminal nerve decreased ventilatory frequency by about 60%; the depressant effect decayed to baseline about 60 s after onset of the stimulus (fig. 5A). Pentobarbitone tonically depressed baseline ventilatory frequency as noted above; phasic stimulation of the trigeminal nerve produced a further depression. In the presence of pentobarbitone, the rate of decay of stimulus-induced depression increased, resulting in a transient overshoot on recovery (fig. 5B). At 10.1 MPa in the presence of pentobarbitone, the spontaneous frequency was depressed further below control values; with phasic stimulation either it did not reduce further, or the rate of decay became too fast to monitor; a transient increase in frequency to greater than prestimulus values was the only effect observed following cessation of stimulation (fig. 5C). In both cases the overshoot reached, but did not exceed, the control (pre-drug) frequency.

DISCUSSION

Use of the newborn preparation

There are several advantages of the isolated newborn spinal cord–medulla preparation: spontaneous and reflex activity remain stable over many hours *in vitro*; normal anatomical connections are preserved; environmental control and manipulation are simple. There are also disadvantages. At the newborn stage, synaptic

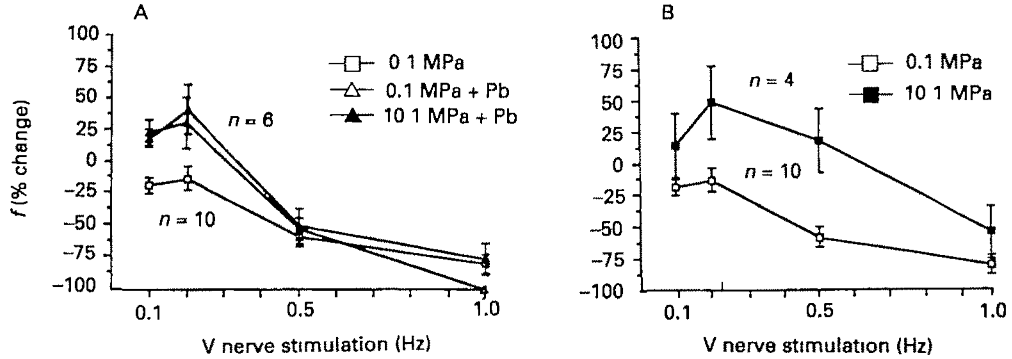

FIG. 4. Effect of pentobarbitone on the spontaneous rhythm modulated by low frequency continuous stimulation of the V (trigeminal) nerve root (mean, SEM). Vertical axes are % change in ventilatory frequency (*f*) from the unstimulated spontaneous frequency. A: At normal pressure (□ = 0 1 MPa), the response to stimulation of the trigeminal nerve was stimulus frequency-related decrease in spontaneous burst frequency. Pentobarbitone 5–8 μmol litre^{-1} changed the response to an increase at low stimulus frequencies ($P < 0.05$). The drug had no effect at stimulus frequencies greater than 0 2 Hz, and pressure had no effect in the presence of pentobarbitone. B: Experiments with pressure alone revealed a similar alteration in the direction of the response to low frequency stimulation at 10.1 MPa ($P < 0.05$ at 0.1–0 5 Hz).

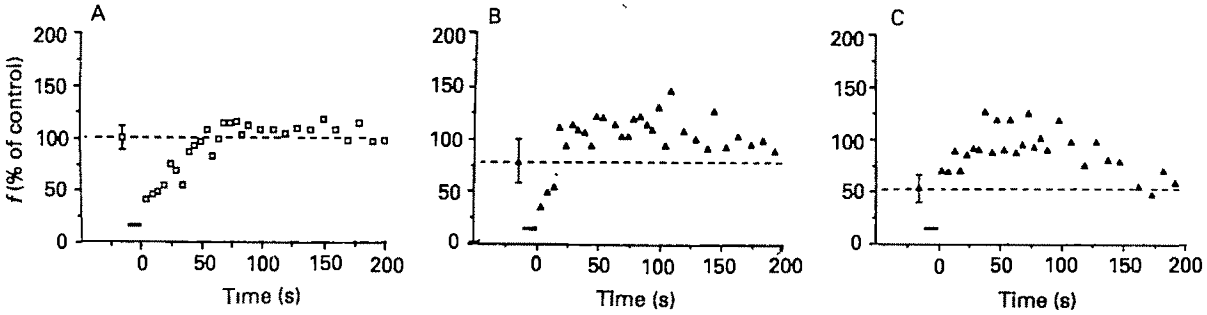

FIG. 5. Response to brief (10-s) high frequency (10 Hz) stimulation (—) of the trigeminal nerve ($n = 7$). A: At normal pressure (0.1 MPa), the spontaneous activity (f) is depressed by stimulation and recovers to control frequencies in about 60 s following cessation of stimulation. B: At normal pressure (0.1 MPa) in the presence of pentobarbitone 5–8 μmol litre^{-1}, the rate of recovery increased and the frequency rebounded above the pre-stimulus value to the drug-free control value (dashed line indicates pentobarbitone-depressed spontaneous frequency) C: Compression to 10.1 MPa in the presence of pentobarbitone either abolished stimulus-induced depression or further increased the rate of recovery to a rebound value greater than the depressed pre-stimulus control (dashed line). The maximum frequency on rebound is again near the drug-free normobaric control value. Control values were measured over the 5 min preceding stimulation, the mean value converted to 100, and SD calculated as percent of the mean. Post-stimulus values were measured over the intervals indicated and expressed as percent of control; SD are omitted for the sake of clarity.

connections in the rat are immature and extrapolation to the adult condition may be difficult. The rather low (27 °C) temperature used may raise concern, but this is the measured rectal temperature of newborn rats when not under the mother. The estimated anaesthetic concentration range for pentobarbitone is 100–600 μmol litre^{-1} [20], although the sedative range may be lower. Both immaturity and low temperature may contribute to the somewhat greater sensitivity to pentobarbitone 5–80 μmol litre^{-1} of the newborn ventilatory output. The absence of sensory feedback in the isolated preparation, however, may be more important.

The rhythmic bursts of activity in ventral roots C_1 and C_5 are clearly identified with ventilatory output [12]. Ventral roots C_5 and C_4 contain the motor neurones of the phrenic nerve, and C_1 those of the accessory muscles of ventilation. Similar rhythmic activity may be recorded from the phrenic nerve itself and can be recorded from C_1 and C_5 *in vivo*. It is not seen in any nerves other than those supplying muscles of ventilation.

Effects of pentobarbitone and pentobarbitone–pressure interactions

The steady state effects of pentobarbitone 5–8 μmol litre^{-1} on spontaneous ventilatory rhythm at normal and hyperbaric pressure are summarized in table I, together with data on the effects of pressure alone taken from a separate study [14]. Pentobarbitone had highly significant depressant effects on both frequency and activity within a single burst, resulting in a reduction in total respiratory drive. The respiratory depressant effects of barbiturates *in vivo* are well known, and it is reasonable to assume that the results of the present study represent some of their *in vitro* correlates.

Pressure alone exerted similar depressant effects on frequency and drive, but not on area [14]. In all cases, the depressant effects of pentobarbitone were greater at 10.1 MPa than at normal (0.1 MPa) pressure. The pressure used, 10.1 MPa, is associated with pressure reversal of anaesthesia in animals. It is also in a range in which dyspnoea occurs with unchanged blood-gas tensions; the change in ventilatory rhythm observed at pressure [21] may be related to this effect. In the case of this complex neural behaviour, as in the case of simpler isolated nerve preparations [5, 9, 22, 23], pressure and an anaesthetic appear to exert similar effects in the same direction rather than antagonism.

Pentobarbitone tended to decrease the inhibitory effects of trigeminal nerve stimulation on the ventilatory rhythm. As in the case of spontaneous rhythm, there was little suggestion of antagonism between pentobarbitone and pressure. Both converted the normal inhibitory response to

TABLE I. *Effects of pentobarbitone (Pb) 5–8 μmol litre^{-1} pressure, (10.1 MPa) and Pb+pressure on respiratory events. Data presented as % change from 0.1 MPa controls. (Data on pressure alone from [14])*

Variable	Pb	Pressure	Pb+ pressure	Conclusions
Frequency	−16% ($n = 15$) $P < 0.01$	−33% ($n = 15$) $P < 0.001$	−38% ($n = 15$) $P < 0.01$	Either no interaction or possible additive effects of HP and Pb
Area	−23% ($n = 10$) $P < 0.001$	— ($n = 11$) ns	−41% ($n = 10$) $P < 0.01$	Synergistic effects of HP and Pb
"Drive"	−34% ($n = 10$) $P < 0.01$	−30% ($n = 11$) $P < 0.05$	−59% ($n = 10$) $P < 0.02$	Additive effects of HP and Pb
Delay C_1–C_8	+3% ($n = 10$) ns	−30.7% ($n = 12$) $P < 0.01$	−23% ($n = 10$) $P < 0.01$	Pentobarbitone has no significant effect at either pressure

trigeminal nerve stimulation to an excitatory response. The effect of the drug at normobaric pressure appeared to be accompanied by an increase in rate of decay of the normal inhibition, leading to rebound excitation not normally observed. The rebound excitation was enhanced at hyperbaric pressure. Both pressure and pentobarbitone slowed spontaneous rhythm; the effect of the rebound following stimulation in each case was to restore the ventilatory frequency to, but not above, its normal spontaneous value. Pentobarbitone blocked additional pressure effects at the greater stimulus frequencies. This result is consistent with an additive effect of pressure and pentobarbitone on the same process.

Mechanism

The present experiments provide little insight into the mechanisms for the additive effects. Generation of ventilatory rhythm is a poorly understood process, even after intensive study over many decades. Components of the process may include intrinsic pacemaker oscillations in individual neurones of the respiratory centres, and excitatory and inhibitory synaptic connections among those neurons and between central respiratory neurones and the motor neurones innervating the muscles of ventilation [24–26]. Barbiturates have biphasic effects on generation of burst discharge in other oscillating nerve cells; at low concentrations they may increase the amplitude and duration of a pacemaker potential, suppressing it at high concentrations [27]. However, barbiturates may also limit burst discharge by increasing spike frequency adaptation [28]. Pressure may decrease an intrinsic pacemaker oscillation frequency by slowing the kinetics of the currents responsible for its initiation and propagation [29–31].

Both pressure and barbiturates depress fast excitatory synaptic transmission mediated by a variety of transmitters [4, 5, 32]. Both may act at least in part by depressing transmitter release [20, 33–36], suggesting a generalized depressant effect on synaptic transmission which may extend to the slower modulatory transmitter actions of both excitation and inhibition. With respect to pressure, most of the depressant effect can be accounted for by depression of transmitter release, and inhibition *per se* is equally depressed with excitation [8]. In contrast, barbiturates have differential postsynaptic effects on excitatory and inhibitory synapses, depressing the excitatory response and enhancing and prolonging GABA-mediated inhibition at the chloride channel [20, 37–40].

Implications

With respect to pressure "reversal" of anaesthesia and anaesthetic inhibition of the seizure component of the high pressure nervous syndrome, anaesthetics and pressure act as antagonists in the intact animal. In dissected neural preparations, however, the basis for antagonism has proved elusive. Evidence for antagonistic interactions is scanty [41, 42]; in many cases pressure and an anaesthetic act in the same direction [23, 43]. We have proposed a hypothesis that normally operating neural networks might support pressure–anaesthetic antagonism because of additive enhancement of facilitation and short-term tetanic potentiation at excitatory synapses. If both pressure and anaesthetics enhance facilitation and potentiation, the result is to overcome the depressant effect of each on excitatory synaptic transmission [9]. Although pressure enhancement of facilitation and potentiation has been shown only in non-mammalian CNS preparations [44, 45], anaesthetic enhancement of potentiation has been demonstrated in both invertebrate and mammalian nervous systems [46].

The rationale for the present studies was that a spontaneously active neural network, rather than one driven by unphysiological stimulation, might exhibit pressure–anaesthetic antagonism. However, the medullary ventilatory oscillator–motor neurone pathway, in common with many simpler isolated neural tissues, exhibits only additive depressant effects of a barbiturate and high pressure. The more such examples are found, the greater becomes the likelihood that pressure–anaesthetic antagonism is peculiar to the central nervous system circuitry that supports awake behaviour and high pressure nervous system seizures. Conversely, it becomes less likely that pressure "reversal" of anaesthesia is caused by direct pressure–anaesthetic antagonism at the molecular level.

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British Journal of Anaesthesia 1991; **66**: 97–102

IN VITRO EFFECT OF ADDITIVES IN BENZODIAZEPINE SOLUTIONS ON THE SUPEROXIDE ANION-GENERATING SYSTEM IN POLYMORPHONUCLEAR LEUCOCYTES

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SUMMARY

Inhibitory effects of diazepam and flunitrazepam on the superoxide anion (O_2^-)-generating system in granulocytes were examined for their clinical relevance. When the effects of commercial solutions and pure preparations were compared using porcine and human polymorphonuclear leucocytes in vitro, *the solutions were found to be more inhibitory than the pure drugs by 4–11 times, indicating that inhibition was caused mainly by the additives in the solutions. Concentrations of the additives required for 50% maximal inhibition of the system were 2.3, 7.5 and 0.9 μl ml^{-1} for propylene glycol, ethanol and benzyl alcohol, respectively, while those of pure diazepam and flunitrazepam were 220 and 190 μg ml^{-1}, respectively, under comparable conditions. However, plasma concentrations of the benzodiazepines and their additives during clinical use were far less than these inhibitory concentrations, indicating that they had no appreciable effect on the O_2^--generating system in polymorphonuclear leucocytes of patients.*

KEY WORDS

Blood neutrophils. Hypnotics benzodiazepines Pharmacology additives, preservatives

Polymorphonuclear leucocytes (PMN) play an important role in the host defence system of mammals against invading micro-organisms. The bactericidal activity of PMN depends at least in part on the ability to generate superoxide anion (O_2^-) and other active oxygen species [1]. The initial reaction—one electron-reduction of molecular oxygen to form O_2^-—is catalysed by an NADPH oxidase which is dormant in the resting cells. Being located in the plasma membrane of PMN, the dormant oxidase is converted to an active state upon phagocytosis or upon stimulation by soluble stimuli, although the precise mechanism(s) for the conversion remain to be elucidated.

It has been speculated that anaesthetic agents affect the immune status of humans and play a role in the occurrence of postoperative infections [2]. Goldfarb and co-workers [3] reported that benzodiazepines inhibited the oxidative activity of human PMN stimulated with zymosan. Subsequently, Nakagawara, Hirokata and Yoshitake [4] reported that neuroleptic agents or i.v. anaesthetics, including diazepam and thiopentone, inhibited O_2^--production in human PMN. They discussed the possibility that benzodiazepines might reduce PMN activity against microbial invasion *in vivo*. In the present study, however, we were not able to observe such inhibitory effects of benzodiazepines (diazepam and flunitrazepam) on the O_2^--generating system in PMN at concentrations reported previously [3, 4]. We then studied effects of the additives contained in their solutions such as propylene glycol, ethanol and benzyl alcohol, and found that these compounds were potent inhibitors of the O_2^--generating system *in vitro*. Accordingly, clinical relevance of the inhibitory effects of the benzodiazepines and their additives has been evaluated. Using porcine PMN, the mechanism(s), by which benzyl al-

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cohol, the most potent inhibitor among the additives, inhibited the O_2^--generating system were also explored.

MATERIALS AND METHODS

Isolation of PMN and solubilization of NADPH oxidase

Porcine and human PMN were isolated by dextran sedimentation, hypotonic lysis and the Ficoll–Conray method as described previously [5] and suspended in HEPES-buffered Hanks' balanced salt solution (composition (mmol litre^{-1}): NaCl 137, KCl 5.4, $MgSO_4$ 0.81, KH_2PO_4 0.44, Na_2HPO_4 0.34, HEPES 25, glucose 5.6; pH 7.4) at 1×10^6 cells ml^{-1}. (This HEPES-buffered medium is designated hereafter as HBSS.) The cell preparation usually contained 95–100% of PMN and showed more than 95% of viability as indicated by trypan blue dye-exclusion test. NADPH oxidase was solubilized with 0.75% octylglucoside from membrane fraction of porcine PMN [6].

Assay of O_2^--production

The O_2^--production was assayed spectrophotometrically by measuring the superoxide dismutase-inhibitable reduction of ferricytochrome *c* at 550 nm as described previously [7, 8]. Suspension of the PMN (2×10^6 cells 2 ml^{-1}) in HBSS described above was incubated for 3 min at 37 °C in a thermostatted cuvette with or without the benzodiazepines and the additives including propylene glycol, ethanol and benzyl alcohol. Then the reaction was initiated by adding one of the following stimulants: 12-*o*-tetradecanoylphorbol-13-acetate (TPA) 0.1 μmol litre^{-1}, lauric acid 400 μmol litre^{-1} and opsonized zymosan 2.5 mg ml^{-1} (final concentrations). TPA was dissolved in dimethylsulphoxide and lauric acid was dissolved in absolute ethanol. The latter solution was neutralized with a minimal amount of NaOH 1 mol litre^{-1} for use [5]. In control experiments, we used xanthine oxidase (Sigma) as the O_2^--generating system [9]. When necessary, O_2^--formation was quantitated further by measuring the formation of compound III of diacetyldeuterohaem-substituted horseradish peroxidase [10]. The viability of PMN before and after exposure to the additives was determined by measuring the release of lactate dehydrogenase (LDH) [11] and by trypan blue dye-exclusion test.

Measurement of plasma concentrations of the additives in patients

Blood samples were obtained from five patients receiving continuous infusion of flunitrazepam for more than 24 h (3–10 ampoules per day) during mechanical ventilation. Plasma concentrations of propylene glycol and benzyl alcohol were determined by gas chromatography (Shimadzu, GC-14A) with butandiol and phenethyl alcohol as internal standards, respectively [12, 13].

Cytosolic free calcium concentration and low temperature spectroscopy

Concentrations of cytosolic free calcium were determined by measuring the changes in Fura2-AM fluorescence according to procedures described elsewhere [14, 15]. Fluorescent changes were monitored with a spectrofluorometer (F-3000 Fluorescence Spectrophotometer, Hitachi) using 340 and 510 nm as excitation and emission wavelength, respectively. Absorption spectra of cytochrome b_{558} in PMN under liquid nitrogen (temperature 77 K) were measured as described previously [16]. The cytochrome was reduced by addition of an appropriate amount of sodium dithionite [16].

Chemicals

Preparations of diazepam 5 mg ml^{-1} and flunitrazepam 2 mg ml^{-1} were obtained commercially. Usually, such a commercial diazepam solution contains about 40% (v/v) propylene glycol, 10% ethanol and other detergents [17]. The injection (1 ml) used in this study contained benzyl alcohol 15.7 mg ml^{-1} in addition to the above ingredients. Similarly, flunitrazepam 1 ml contains ethanol 159 mg, benzyl alcohol 30 mg and propylene glycol 809 mg [18]. A mixture of additives, which contained exactly the same ingredients as above except for flunitrazepam, was used for control experiments. Pure preparations of diazepam and flunitrazepam were the gifts of Takeda Chemical Industries, Ltd and Eisai Chemical Industries, Ltd, Japan, respectively, and were used as dimethylsulphoxide solution. Concentrations of the additives were expressed in % (v/v) in this study. The specific gravities of the additives, used for calculations, were 1.036, 0.789 and 1.042 for propylene glycol, ethanol and benzyl alcohol, respectively [19]. Pure lauric acid was a gift of Nippon Oil & Fats Co., Japan [5]. All other chemicals were of the highest grade commercially available.

RESULTS

Effects of flunitrazepam, diazepam and their injections on O_2^--formation in porcine PMN

We compared the effects of a flunitrazepam injection, a mixture of the additives which mimicked the composition of the injection (77% propylene glycol, 20% ethanol and 3% benzyl alcohol), and pure flunitrazepam dissolved in dimethylsulphoxide on the O_2^--production in porcine PMN. Throughout the experiments, TPA dissolved in dimethylsulphoxide was used as the stimulant. Dimethylsulphoxide up to 0.4% in the reaction mixture showed no inhibitory effect on O_2^--production, which was inhibited by all of the above solutions in a dose-dependent manner (fig. 1). Concentrations of the solution, the additive mixture and pure flunitrazepam to give a half maximal inhibition (K_i) were 9 µl ml^{-1}, 8 µl ml^{-1} and 190 µg ml^{-1}, respectively. It should be noted that 9 µl of the injection contained only 18 µg of flunitrazepam, which was less than 10% of the K_i value for pure flunitrazepam (190 µg ml^{-1}). These results indicated that the inhibitory effect of the flunitrazepam injection was caused mostly by additives. Similarly, the K_i of pure diazepam was 220 µg ml^{-1}, in contrast with that of 10 µl ml^{-1} for the injection, which contained 50 µg of the drug. (In a previous study [3], the K_i values of flunitrazepam and diazepam were reported to be 56 and 13 µg ml^{-1}, respectively, which were rather closer to the values obtained using the solutions than to those obtained with pure drugs in this study.)

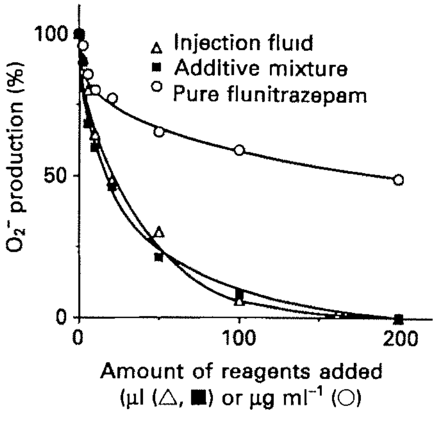

FIG 1. Effects of flunitrazepam and its additives for injection on O_2^--formation in PMN. For experimental conditions including assay method, reaction mixture (2 ml in total volume) and composition of the mixture of additives, see Materials and Methods. After 3 min of incubation with the indicated amount of the reagents, O_2^--formation was initiated by the addition of 12-*o*-tetradecanoylphorbol-13-acetate 0.1 µmol litre^{-1}. Values are percent of control (O_2^--forming activity obtained without the reagents (mean 4.7 (SEM 0.5) nmol min^{-1} 10^6 cells^{-1}, $n = 3$)).

Effects of the additives on the O_2^--formation in porcine and human PMN

In the next series of experiments, effects of each additive (propylene glycol, ethanol and benzyl alcohol) on O_2^--formation were examined by using both human and porcine PMN. The cells were stimulated by three types of stimulants: opsonized zymosan, TPA and laurate. The additives were found to be strong inhibitors of the O_2^--generation systems, and the inhibition occurred irrespective of the type of stimulus. These inhibitions were confirmed using an alternative assay method with diacetyldeuterohaem-substituted horseradish peroxidase [10]. The results, expressed as apparent inhibition constants (K_i) of these additives show benzyl alcohol to be the most potent inhibitor (table I).

When PMN were incubated for 3 min with one of these additives at a saturated concentration and washed with an additive-free HBSS, more than 85% of the original activity was found to be restored. Thus all these inhibitions were reversible. Under these conditions, less than 1% of total LDH was released from the PMN. On the other hand, these additives had no inhibitory effect on O_2^--generation by xanthine oxidase (data not shown), indicating that the additives did not scavenge O_2^- or interfere with the reaction of O_2^- with ferricytochrome *c*. Furthermore, concentrations of the stimuli required for a half-maximal activation were almost unaffected by these additives: 0.7 and 1.0 nmol litre^{-1} for TPA, 380 and 420 µmol litre^{-1} for lauric acid, and 0.83 and 1.0 mg ml^{-1} for opsonized zymosan, in the absence and presence of 0.1% benzyl alcohol, respectively. Similar results were obtained with other additives. These findings suggest that the additives did not alter the potency of the stimulants to induce O_2^--production.

Blood concentrations of the additives in patients

To evaluate the effect of the additives *in vivo*, we determined the plasma concentrations of propylene glycol and benzyl alcohol in patients

TABLE I. *Mean* (SEM) K_i *values of propylene glycol, ethanol and benzyl alcohol for* O_2^-*-production in porcine and human PMN. Concentrations of the additives required for a half maximal inhibition* (K_i) *were expressed as % (v/v) in the reaction mixture. Experimental conditions were as in figure 1. Mean* (SEM) *control activities of* O_2^-*-production were 2.5 (0.6), 8.8 (2.1), 3.1 (0.6) and 4.0 (0.8) nmol* min^{-1} 10^6 $cells^{-1}$ (n = 3), *as induced by opsonized zymosan 2.5 mg* ml^{-1}, *TPA 0.1 µmol* $litre^{-1}$ *or lauric acid 400 µmol* $litre^{-1}$ *in porcine PMN and by TPA 0.1 µmol* $litre^{-1}$ *in human PMN, respectively*

Stimulant	K_i (%) Propylene glycol	Ethanol	Benzyl alcohol
Porcine			
Opsonized zymosan	1.03 (0.08)	0.60 (0.05)	0.04 (0.01)
TPA	0.23 (0.01)	0.75 (0.12)	0.09 (0.02)
Lauric acid	1.13 (0.03)	0.85 (0.14)	0.14 (0.04)
Human			
TPA	0.53 (0.03)	1.16 (0.05)	0.13 (0.02)

during steady state continuous infusion of flunitrazepam (3–10 ampoules per day). The blood samples were collected from five patients, and, in all those tested, the plasma concentrations of propylene glycol and benzyl alcohol were less than the limit of detection ($< 5 \times 10^{-5}$ %) with our assay system.

Mechanisms of inhibition by benzyl alcohol

In an attempt to clarify the mechanisms by which benzyl alcohol, the strongest inhibitor among the additives, acts on the O_2^--generating system in PMN, we investigated the effects of the alcohol on a solubilized NADPH oxidase preparation [6] and on the spectrum of cytochrome b_{558} in intact cells. When a solubilized enzyme preparation from porcine PMN was used for the experiments, the mean (SEM) activity of NADPH-dependent O_2^--production was 275 (30) nmol min^{-1}/mg of protein ($n = 3$). Benzyl alcohol inhibited the O_2^--production catalysed by such a preparation in a dose-dependent manner (K_i 0.4%). On the other hand, the K_m value of this solubilized oxidase for NADPH 28 µmol $litre^{-1}$ was not affected by the alcohol.

We studied next the effects of benzyl alcohol on cytochrome b_{558} in intact porcine PMN using spectroscopy. Cytochrome b_{558} is known to be a key component of the O_2^--generating system in PMN [1]. The α-band of the reduced state of the cytochrome showed a sharp peak at 558 nm, with a shoulder at 556 nm (fig. 2). Upon addition of 1% benzyl alcohol, the α-band was reduced in height and the previously sharp peak at 558 nm was flattened. The original profile of the spectrum was restored, however, on removal of benzyl alcohol by washing the PMN with HBSS (spectrum not shown). These results indicate that benzyl alcohol interacted directly with NADPH oxidase, a multi-component enzyme system, to inhibit the reaction. Finally, we examined effects of benzyl alcohol on the changes in cytosolic free calcium concentration in intact cells during the activation. The mean (SEM) basal level of the calcium concentration monitored by Fura2-

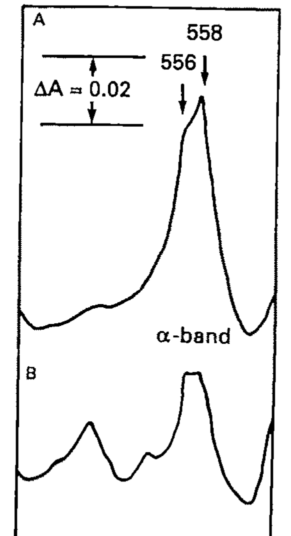

FIG. 2. Effect of benzyl alcohol on absorption spectrum of cytochrome b_{558} in porcine PMN. Porcine PMN (2×10^8 cells ml^{-1}) were suspended in phosphate-buffered saline 10 mmol $litre^{-1}$ (pH 7.4) containing 30% glycerol, and the spectra were recorded at 77 K after an appropriate addition of sodium dithionite. For other details, see Materials and Methods. A: In the absence of benzyl alcohol; B: in the presence of 1% benzyl alcohol.

fluorescence in resting cells was 119 (4) nmol litre^{-1} ($n = 3$), which increased to 202 (8) nmol litre^{-1} ($n = 3$) upon stimulation with lauric acid 400 µmol litre^{-1}. Benzyl alcohol up to 2 % had no effect on either basal or increased concentrations of calcium, indicating that the alcohol did not affect calcium mobilization, an important process involved in the signal transduction pathway for PMN activation [20].

DISCUSSION

Many clinically used drugs for injection, in particular water-insoluble drugs, contain additives such as propylene glycol and ethanol to increase both solubility and stability of the drugs. Sometimes, analgesics and preservatives such as benzyl alcohol are also included. Solutions of diazepam and flunitrazepam, used frequently as anaesthetics for induction of general anaesthesia, sedatives during mechanical ventilation and anticonvulsants, also contain these additives. In this study, we demonstrated that diazepam and flunitrazepam were less potent inhibitors of the O_2^--generating system in PMN than reported previously [3, 4]. The K_i values of diazepam and flunitrazepam measured with both human and porcine PMN (about 200 µg ml^{-1} for both benzodiazepines) were much larger than the plasma concentrations of these drugs observed in patients (< 1 and < 0.03 µg ml^{-1}, respectively) [21, 22], indicating that the benzodiazepines are unlikely to have an effect on the O_2^--generating system in PMN of patients receiving these drugs.

On the other hand, commercial preparations of diazepam and flunitrazepam exerted much stronger inhibitory effects *in vitro* than those expected from their drug contents, indicating that the observed inhibition was caused largely by the additives in the solutions, rather than the drug itself. In fact, the inhibition curve with the additive mixture was almost identical to that with the injection (fig. 1). These results suggest that previous workers [3, 4] mistook the effects of additives for those of the drugs, although they did not state if they had used pure benzodiazepines or commercial solutions. In addition, the steady state plasma concentrations of propylene glycol and benzyl alcohol in patients were so small that we could not detect them in all five patients receiving continuous infusion of commercial flunitrazepam. Furthermore, the inhibitions were reversible. For all these reasons we concluded that the additives and the benzodiazepines themselves could not have significant effects on the O_2^--generating system in PMN in patients.

The mechanisms by which the additives inhibit the O_2^--generating system *in vitro* is of interest. The inhibition took place regardless of the type of stimulus, such as soluble or particulate, suggesting that the inhibition was not caused by prohibition of phagocytosis. The additives did not depress the ability of the stimulants to induce O_2^--production or interfere with the reaction of O_2^- with ferricytochrome *c*. Furthermore, no significant release of LDH was observed upon exposure of the cells to the additives, indicating that the inhibition was not caused by increased permeability of the cell membranes. These results, taken together, indicated that the additives inhibited the O_2^--production by affecting either the O_2^--generating system itself or its activation in the cell. We then studied the mechanisms of inhibition caused by benzyl alcohol, the most potent inhibitor among the three additives. The results revealed that benzyl alcohol could inhibit the solubilized NADPH oxidase system, where the possible site of inhibition was at cytochrome b_{558}. These findings, together with the fact that intracellular calcium mobilization upon activation of the system was not affected by benzyl alcohol, indicated that benzyl alcohol inhibited NADPH oxidase directly by affecting the component(s) of this multienzyme system. A similar inhibitory effect of organic solvents such as pyridine has been reported [23].

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DISPOSITION OF MORPHINE-6-GLUCURONIDE AND MORPHINE IN HEALTHY VOLUNTEERS

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SUMMARY

The pharmacokinetics and subjective side effects of i.v. morphine sulphate 120 μg kg^{-1} and morphine-6-glucuronide (M6G) 30 μg kg^{-1} were determined in six healthy volunteers, using a placebo-controlled, single-blind randomized crossover design. Five of these volunteers underwent an additional (non-randomized) study of M6G 60 μg kg^{-1}. Subjective side effects were similar following both drugs, but of shorter duration following M6G. Morphine was not detected after administration of M6G. For M6G 30 μg kg^{-1} the mean (SD) volume of distribution, elimination half-life and clearance were 29.38 (18.36) litre, 2.05 (1.2) h and 187.81 (37.41) litre h^{-1}, respectively. These values were not significantly different from those obtained for M6G 60 μg kg^{-1}. In all subjects the volumes of distribution and clearances were significantly smaller for M6G than for morphine, but the elimination half-lives were similar.

KEY WORDS

Analgesics. morphine, morphine-6-glucuronide. Pharmacokinetics morphine, morphine-6-glucuronide

Pharmacologically active metabolites are of great interest to clinicians as they may augment or inhibit the effects of the parent drug, or enhance its toxicity [1]. Morphine-6-glucuronide (M6G) may make a significant contribution to the apparent analgesic efficacy of morphine [2–4], although previous authors have estimated that only 0.3–6.4% of administered morphine is recovered in urine as this metabolite [5, 6].

M6G has avid affinity for mu 1 and mu 2 receptors, to which it binds stereospecifically with an affinity similar to that of morphine [7, 8]. In rodents, M6G administered by the subcutaneous or intracerebral routes has a greater analgesic potency and a longer duration of action than morphine [9], and on direct injection into the peri-aqueductal grey matter it is 20 times as potent [8].

It is desirable to have a full understanding of the disposition and clinical effects of a pharmacologically active metabolite. In order to obtain this, it is necessary to administer the metabolite independently of the parent drug and thereby determine its volume of distribution, clearance and half-life. It may then be possible to calculate the percentage of the parent drug which is converted to the metabolite and enters the plasma compartment.

The object of this study was to obtain data on the disposition of M6G, together with its subjective effects in volunteers, and to compare them with those of morphine.

SUBJECTS AND METHODS

Six healthy subjects (three male, mean (SD) age 30.6 (2.5) yr, mean (SD) weight 68.3 (8.7) kg) gave informed consent to the study, which was approved by the hospital Ethics Committee. Each subject received morphine sulphate 120 μg kg^{-1}, M6G 30 μg kg^{-1} and placebo (isotonic saline) on three non-consecutive mornings, in accordance with a randomized single-blind crossover design. Five of these subjects underwent an additional, single-blind, non-randomized study of M6G 60 μg kg^{-1}.

An i.v. cannula was inserted into each arm, and test drugs given over 4 min. Venous samples were obtained (from the contralateral arm) at 5, 10, 20,

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40, 80, 160 and 320 min after injection of each test drug. Plasma was separated by immediate centrifugation and stored at −70 °C until analysed for morphine and M6G concentrations. Adverse reactions during or following the study were assessed by direct questioning, and the times to complete recovery were recorded.

Plasma concentrations of morphine and M6G were analysed simultaneously using high pressure liquid chromatography with recommended modifications [10, 11]. The standards used were morphine sulphate (McFarland Smith) and M6G (Ultrafine Chemicals). Calibration curves were constructed daily for both drugs, and were linear with correlation coefficients greater than 0.9970. The limit of detection for morphine and M6G was 1 ng ml^{-1}.

Kinetic calculation

Plasma morphine and M6G concentration–time data were analysed using an interactive curve-stripping program, using weighted non-linear least square regression analysis [12, 13]. For morphine (M) and directly injected M6G (M6G) the data were fitted to a two-compartment model in all subjects. For analysis of M6G concentrations occurring as a result of morphine metabolism (M6Gi), a one-compartment model was used. The areas under the concentration–time curves were calculated using the trapezoid rule and extrapolations to infinity estimated using the terminal elimination half-lives of the respective curves. The following kinetic parameters were obtained:

$T_{\frac{1}{2}}$M(h)	Terminal half-life for morphine
AUCM_{0-320}(ng h litre^{-1})	Area under the concn–time curve for morphine (0–320 min)
AUC$\text{M}_{0-\infty}$(ng h litre^{-1})	Area under the concn–time curve for morphine (0 to infinity)
Vd^{ss}M(litre)	Volume of distribution for morphine
ClM(litre h^{-1})	Clearance for morphine
$T_{\frac{1}{2}}$M6G(h)	Terminal half-life for M6G
AUCM6G_{0-320}(ng h litre^{-1})	Area under the concn–time curve for M6G (0–320 min)
AUC$\text{M6G}_{0-\infty}$(ng h litre^{-1})	Area under the concn–time curve for M6G (0 to infinity)
Vd^{ss}M6G(litre)	Volume of distribution for M6G
ClM6G(litre h^{-1})	Clearance for M6G
AUCM6Gi_{0-320}(ng h litre^{-1})	Area under the concn–time curve for M6Gi (0–320 min)
AUC$\text{M6Gi}_{0-\infty}$(ng h litre^{-1})	Area under the concn–time curve for M6Gi (0–infinity)

The fraction (FM) of the i.v. dose of morphine metabolized to M6G and appearing in the plasma was calculated from equation (1), and the ratio of the elimination rate constants for M6G and morphine (kM6G: kM) calculated from equation (2) [1]:

$$F\text{M} = \text{AUCM6Gi}_{0-\infty}/\text{AUCM}_{0-\infty} \times Cl\text{M6G}/Cl\text{M} \tag{1}$$

$$k\text{M6G}:k\text{M} = \frac{Cl\text{M6G}/Cl\text{M}}{Vd\text{M6G}/Vd\text{M}} \tag{2}$$

Statistical methods

The results, presented as mean (SD) and range, were analysed using the Mann–Whitney U test, with $P < 0.05$ being taken as the minimum level of significance.

RESULTS

Kinetic data

In all subjects M6Gi was detected in plasma within 10 min of administration of morphine. The concentrations reached were greater than those of morphine at, and at all times after, 80 min. Morphine was not detected after administration of M6G.

Mean plasma concentration–time curves for morphine, M6Gi and M6G at the two doses investigated are shown in figure 1. The elimination half-lives ($T_{\frac{1}{2}}^{\beta}$) for morphine and M6G were similar, but the apparent volumes of distribution and total body clearances were significantly smaller for M6G than for morphine ($P < 0.05$) (table I). The mean (SD) percentage of morphine metabolized to M6Gi (FM) was 11.5

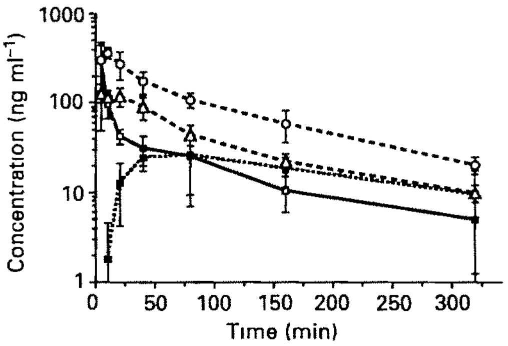

FIG. 1. Semi-logarithmic plots of morphine and morphine-6-glucuronide concentrations in normal volunteers. □ = Morphine sulphate 120 µg kg^{-1} ($n = 6$); △ = morphine-6-glucuronide 30 µg kg^{-1} ($n = 6$), ○ = morphine-6-glucuronide 60 µg kg^{-1} ($n = 5$); ■ = morphine-6-glucuronide following morphine.

TABLE I. *Pharmacokinetic parameters for i.v. morphine and morphine-6-glucuronide (mean* (SD) *[range])*

	Morphine 120 μg kg^{-1}	M6Gi	M6G 30 μg kg^{-1}	M6G 60 μg kg^{-1}
*C*max (ng litre^{-1})	302.1 (163.9) [105.4–531.8]	28.83 (16.08) [16.0–60.4]	155.47 (49.26) [101.4–236.6]	414.44 (29.84) [375.3–451.2]
$T_{\frac{1}{2}}$ (h)	2.03 (1.35) [0.9–3.86]	1.88 (1.28) [0.66–4.21]	2.05 (1.20) [0.62–3.40]	1.81 (0.75) [1.03–2.99]
$AUC_{0-\infty}$ (ng h litre^{-1})	139.3 (48.9) [84.1–199.7]	96.7 (71.16) [46.2–190.3]	208.8 (55.4) [144.0–275.0]	514.8 (100.2) [353.0–619.0]
AUC_{0-320} (ng h litre^{-1})	116.1 (44.16) [73.4–188.5]	58.13 (50.75) [21.0–137.4]	177.19 (47.37) [117.9–246.8]	455.1 (98.71) [295.84–568.32]
Cl (litre h^{-1})	1057.4 (498.8) [667.6–2022.7]		187.8 (37.4) [126.2–230.8]	127.4 (37.1) [99.0–189.0]
Vd^{**} (litre)	180.6 (81.5) [72.4–287.6]		29.4 (18.4) [8.7–54.8]	19.3 (7.5) [12.3–30.3]

TABLE II. *Subjective side effects of morphine and morphine-6-glucuronide*

	Placebo (*n* = 6)	Morphine 120 μg kg^{-1} (*n* = 6)	M6G 30 μg kg^{-1} (*n* = 6)	M6G 60 μg kg^{-1} (*n* = 5)
Light headedness	1/6	6/6	6/6	5/5
Sedation	1/6	6/6	4/6	4/5
Nausea	0/6	5/6	0/6	2/5
Itching	0/6	2/6	0/6	0/5
Rash	0/6	2/6	0/6	0/5
Heavy/aching muscles	0/6	3/6	4/6	4/5
Mean (SD) time to complete recovery (h)	0	15 (5)	4 (1)	6 (2)

(9.1)% as calculated from concentration–time data extrapolated to infinity (molar ratios).

Subjective side effects

All volunteers reported some subjective side effects after both morphine and M6G, but the time taken for full recovery was shorter after M6G (table II).

DISCUSSION

The most striking aspect of M6G among the opioids is its small volume of distribution (< 0.5 litre kg^{-1}) and low clearance. This is apparent from the initial high plasma concentrations and gradual decay.

The results of the present study demonstrate that the terminal half-life of M6Gi is not significantly different from the terminal half-life of the parent drug or M6G administered directly. The only reported previous pharmacokinetic study of i.v. M6G in man with normal renal function (one patient following 1 mg/70 kg) [2] gave a terminal elimination half-life of about 2 h, which is in accordance with our findings.

As the concentration of M6Gi declines in parallel with morphine in the terminal phase, one may deduce that the elimination rate constant for M6Gi is greater than that of morphine, and that the decay of the concentration–time curve for M6Gi is limited by the rate of formation of M6Gi [1].

Previous studies have demonstrated the appearance of M6G in human CSF following oral and parenteral administration of morphine [3]. It is intriguing that an opioid, which is highly polar and less lipophilic than morphine, is able to penetrate the blood–brain barrier, as has been shown in animals and man [3, 14]. There is no identifiable system for active transport of M6G into CSF, nor any evidence for its metabolism in the CNS *in vivo* [15, 16], although human neural tissue is capable of catalysing the conversion of morphine to M6G *in vitro* [17]. Diffusion of a drug across the blood–brain barrier is dependent on the plasma–brain concentration gradient of the unbound fraction, and the lipid solubility, degree of ionization and molecular conformation at physiological pH.

Our results show that the plasma volume is greater than 10% of the total volume of distribution of M6G, and the ratio of the plasma volume to the total volume of distribution ($V_P:\mathrm{Vd}^{tot}$) for M6G is five times greater than the $V_P:Vd^{tot}$ ratio for morphine. The high concentrations of this metabolite present in the plasma compartment may facilitate penetration into the CNS. The terminal half-life of intrathecally administered M6G in CSF exceeds that of morphine [16], a further factor contributing to its therapeutic importance.

The half-lives of M6Gi and M6G are prolonged in patients with impaired renal function [2, 18] and an increase in AUC for M6Gi in anaesthetized patients (caused probably by decreased renal blood flow) has been reported [19]. The reduction in plasma proteins and alterations in their binding characteristics which occur in renal insufficiency [1] may contribute further to increased concentrations of free M6G. These considerations underline the relevance of M6G in producing toxicity in these patients, particularly in relation to respiratory function [21, 21].

M6G exerts an inhibitory action on C-fibre evoked potentials in the rat spinal cord after both direct application and systemic injection [22]. Its potency in this model was 13 times that of morphine, and in man intrathecal M6G has a greater potency than intrathecal morphine [16]. These findings, together with its interesting pharmacokinetic profile and low incidence of side effects, warrant further investigation to establish the relative analgesic potency of i.v. M6G in man.

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EFFECT OF CLONIDINE ON THE CIRCULATION AND VASOACTIVE HORMONES AFTER AORTIC SURGERY

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SUMMARY

After completion of abdominal aortic graft, 29 patients received an i.v. infusion of placebo (n = 16) or clonidine 7 µg kg^{-1} (n = 13) over 120 min in a double-blind study. Cardiovascular variables were measured and plasma samples obtained up to 5 h after arrival in the recovery room, for assay of noradrenaline, adrenaline, vasopressin and renin concentrations. Noradrenaline, adrenaline and vasopressin concentrations decreased in the clonidine group throughout recovery (P < 0.001, 0.05 and 0.05, respectively, vs placebo). Heart rate was less in the clonidine group (P < 0.01). There was no significant difference in mean arterial pressure between groups. Stroke volume was larger (P < 0.01) and there were fewer episodes of hypertension (P < 0.05) and tachycardia in the clonidine group. In addition, a reduction in the number of circulatory interventions (P < 0.05) and episodes of shivering was noted in the clonidine group. Mean (SD) postoperative volume requirements were larger in the clonidine group (total postoperative input: clonidine 1462 (604) ml; placebo 1064 (348) ml (P < 0.05)). These data are consistent with the observation that clonidine modifies endocrine and circulatory status after major surgery.

KEY WORDS

Hormones adrenaline, noradrenaline, renin, vasopressin Surgery: aortic Sympathetic nervous system clonidine.

Tachycardia or hypertension after aortic surgery may be a consequence of increased concentrations of vasoactive hormones. An α_2-adrenergic agonist, clonidine (Catapres), has been shown to attenuate central and peripheral sympathetic and circulatory hyperactivity in several situations [1–8]. Clonidine also decreases plasma concentrations of catecholamines, vasopressin [9] and renin [10]. We have studied the effect of clonidine on vasoactive hormones and cardiovascular state after aortic surgery.

PATIENTS AND METHODS

The study was approved by the Ethics Committee and informed patient consent was obtained. On the morning of surgery, all patients with a history of hypertension (defined as an arterial pressure exceeding 160/95 mm Hg for more than 6 months), or coronary artery disease or heart failure received all their concurrent medication, including calcium entry blocking (CEB) agents. Diuretics were omitted. Patients receiving centrally-acting antihypertensives, including clonidine, were not excluded: one patient in the placebo group was receiving low dose clonidine therapy (150 µg daily). The subjects (all male) were allocated randomly in a double-blind manner to two groups before surgery by means of a random table generated by a computer. The placebo group received a normal saline infusion shortly after aortic declamping ($n = 16$) and the clonidine group ($n = 15$) received clonidine

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7 µg kg^{-1} as an infusion of identical volume over a similar period (120 min). Two patients in the clonidine group were withdrawn from the trial for surgical reasons.

Cardiovascular data and plasma samples were collected at the following stages: immediately after vascular catheterizations and before induction of anaesthesia (baseline); immediately before infusion of clonidine (5–10 min after bilateral aortic declamping and volume replacement and cardiovascular stabilization); upon arrival in the recovery room (RR) immediately after repositioning and recalibration of the same transducer-amplifier system and treatment of any acute cardiovascular disturbance (R1). All patients treated chronically with CEB received nifedipine 10 mg intranasally (i.n.) immediately after arrival in the recovery room. Further data and plasma samples were collected every 1 h for 5 h thereafter (R2–R6). The lungs of all patients were ventilated mechanically with 50% oxygen during the postoperative study period to a Pa_{CO_2} of 4–5.3 kPa. Gases were humidified and warmed. Temperature was monitored from the thermistor of the pulmonary artery catheter and maintained with a heated mattress.

Circulation

The ECG was monitored using the CM5 lead. Radial and pulmonary arterial catheters were inserted under local anaesthesia and the zero was set at the midthoracic level. Cardiac output (CO) was measured by thermodilution in triplicate with less than 10% variation. Derived indices were calculated according to standard formulae. Systolic arterial pressure (SAP) and heart rate (HR) were maintained within 20% of baseline values throughout the study. Tachycardia and bradycardia were defined as > 100 and < 45 beat min^{-1}, respectively. Hypo- or hypertension were defined as SAP < 90 or > 170 mm Hg. Warmed colloid and crystalloid solutions were administered throughout surgery and recovery to maintain pulmonary capillary wedge pressure (PCWP) 1–5 mm Hg greater than baseline values. Tachycardia was treated with propranolol 0.5 mg i.v. every 5 min until HR was consistently less than 100 beat min^{-1}. Hypertension was treated with nifedipine 10 mg i.n. repeated every 10–20 min until SAP was consistently less than 170 mm Hg. Hypotension of slow onset was treated with crystalloid 500 ml over 20 min. When hypotension, bradycardia, or both, occurred suddenly, phenylephrine 100 µg, atropine 0.5 mg or both were administered, followed by a volume challenge if the PCWP measured simultaneously was less than the baseline value.

Anaesthesia

Flunitrazepam 20 µg kg^{-1} and pancuronium 100 µg kg^{-1} were given at induction of anaesthesia. Fentanyl was given at induction (6 µg kg^{-1}), incision (3 µg kg^{-1}) and throughout surgery (4 µg kg^{-1} h^{-1}). The total dose of fentanyl was 50 µg kg^{-1} in both groups. Seventy percent nitrous oxide in oxygen and pancuronium (as required) were given during maintenance. After operation, patients were sedated with morphine 10 mg s.c., flunitrazepam 1 mg i.v., or both, as required.

Plasma samples

Plasma concentrations of catecholamines were measured in duplicate by a double isotope radioenzymatic technique [11]. The sensitivity of the assay was 25 pg ml^{-1} for adrenaline and noradrenaline. Intra-assay coefficient of variation was 8% and inter-assay coefficient of variation was 12%. Normal values are 30–90 pg ml^{-1} for adrenaline and 300–900 pg ml^{-1} for noradrenaline in this laboratory.

A radioimmunological assay [12] was used to measure vasopressin (AVP) in duplicate, with a sensitivity of 0.5 pg ml^{-1}. Mean (SD) recovery of AVP was 75 (3)%. Intra-assay coefficient of variation was 13% and inter-assay coefficient of variation was 18%; normal values are 0.5–6.0 pg ml^{-1}.

Active plasma renin concentration was measured with an immunoradiometric assay (Renin RIA, Diagnostics Pasteur [13]). The sensitivity was 10 pg ml^{-1} and recovery 97–105%. Intra-assay coefficient of variation was 3.1–6.1% and inter-assay coefficient of variation was 4.8–8.0%; the normal range of values in the recumbent healthy volunteer is 10–25 pg ml^{-1}.

Plasma concentrations of clonidine were measured with a radioimmunoassay [14]. The detection limit was 10 pg ml^{-1}, intra-assay coefficient of variation 4% and inter-assay coefficient of variation 8.3%. Sodium (Na^+) and potassium (K^+) concentrations were measured using indirect potentiometry (Astra Analyzer, Beckmann). Plasma osmolarity was measured by a freezing point depression osmometer (Osmomat 030, Gonotech). Arterial and mixed venous samples were withdrawn simultaneously at a rate of 1.5 ml min^{-1} and kept at +4 °C.

Statistical analysis

Data are reported as mean (SD) unless stated otherwise. Clinical data were compared using chi-square test and Wilcoxon's two-sample test as appropriate. Endocrine and circulatory variables were analysed by three methods. Data obtained at baseline and immediately before the beginning of infusion were compared by one-way analysis of variance testing for a treatment effect. Data obtained from the beginning of infusion up to R6 were considered as the postoperative period and compared by analysis of variance for repeated measures, testing for treatment and time factors and their interaction. In the case of significant interaction, the main effect of time was considered at each level of the treatment factor—that is, in each group of patients. In the case of a significant treatment effect, no pairwise comparison at each interval was attempted, as the major aim of the study was to assess the overall evolution of the variables between groups during the postoperative period (from the beginning of infusion to the end of recovery). In the case of non-significant time–treatment interaction, the result of a main effect was considered. Data obtained at baseline and R6 were considered as the perioperative period and compared using identical procedures. $P < 0.05$ was considered significant.

RESULTS

The groups were similar for patient (table I), cardiovascular and endocrine variables and intra-operative surgical, anaesthetic and fluid management. There was a greater number of untreated or inadequately treated hypertensive patients in the placebo group, but this was not statistically significant. The number of patients receiving CEB was greater in the placebo group (placebo 11, clonidine 1). Duration of surgery was longer in the placebo group ($P < 0.05$). However, cross-clamp times were similar between groups. Blood-gas tensions, Na^+ and K^+ concentrations, osmolarity and temperature were similar in the two groups throughout the study.

TABLE I. *Patient data (mean SD). ASA = American Society of Anesthesiology; CHF = Canadian Heart Foundation; NYHA = New York Heart Association; ACBP = Aorto-coronary bypass; TIA = transient ischaemic attacks; COPD = chronic obstructive pulmonary disease. *As reported by the patient at time of preoperative consultation. †Some patients had two diagnoses*

	Placebo	Clonidine
n	16	13
Age (yr)	58.7 (8.9)	52.5 (9.9)
Height (cm)	169.8 (6.9)	171.0 (8.4)
Weight (kg)	68.4 (14.2)	69.3 (11.5)
ASA I	0	1
II	10	9
III	5	3
IV	1	0
NYHA 0	7	6
I	8	5
II	0	1
III	1	1
CHF 0	14	13
I	0	0
II	2	0
Hypertension	9	5
Duration (yr)	15.6 (3.9)	3.5 (5.3)
Greatest value (mm Hg)*	228 (47)	190 (22)
Poorly controlled (> 180/110 mm Hg)	2	0
Ward SAP (mm Hg)	151 (31)	135 (17)
DAP (mm Hg)	94 (13)	81 (9)
HR (beat min^{-1})	76 (9)	73 (9)
Myocardial infarction	2	0
Previous ACBP	1	0
Previous stroke/TIA	4	3
COPD	8	4
Diabetes	2	1
Alcohol abuse	5	6
Surgical diagnosis†		
Aortic occlusive disease	9	10
Abdominal aortic aneurysm	7	4
Other	1	0

Postoperative course

Analgesic/sedative requirements and requirements for fluid volume, atropine or vasopressor treatment were similar between groups (table II). In the placebo group, nine patients presented before operation with hypertension and 12 patients became hypertensive after operation. In the clonidine group, five patients presented before operation with hypertension and three patients became hypertensive after operation. The clonidine group had a lower incidence of hypertension ($P < 0.05$), tachycardia, number of nifedipine/propranolol interventions ($P < 0.05$), total number of vasoactive interventions ($P < 0.05$) and shivering (table II). Volume requirements were larger in the clonidine group (total input: clonidine group 1462 (604) ml; placebo group 1064 (348) ml) ($P < 0.05$). No patient experienced delayed awakening or needed prolonged mechanical ventilation.

TABLE II. *Postoperative events. †Hypo/hypertension = SAP less than 90 mm Hg or greater than 170 mm Hg, respectively, for 10 min or more; bradycardia/tachycardia = HR less than 45 beat* min^{-1} *for 5 min or greater than 100 beat* min^{-1} *for 10 min or more, respectively. ‡Circulatory interventions: inotrope, volume challenge, vasopressor, atropine, propranolol or nifedipine. *Hypotension and bradycardia occurred in one patient*

	Placebo ($n = 16$)	P	Clonidine ($n = 13$)
Shivering			
Number of episodes	12		3
Number of patients having at least one episode	7 (47%)	ns	3 (23%)
Mean number of episodes per patient	0.80 (1.01)	ns	0.23 (0.44)
Hypotension–bradycardia†			
Number of patients having at least one episode	2	ns	2*
Smallest cardiac output (litre min^{-1})	3.97 (1.60)	ns	3.70 (1.16)
Slowest HR (beat min^{-1})	73 (16)	ns	60 (13)
Greatest ($Ca_{O_2} - Cv_{O_2}$) (vol dl^{-1})	6.83 (2.25)	ns	5.88 (1.01)
Hypertension–tachycardia†			
Number of episodes of hypertension	30		7
Number of episodes of tachycardia	18		2
Mean number of episodes of hypertension per patient	1.87 (1.93)	< 0.05	0.46 (0.66)
Mean number of episodes of tachycardia per patient	1.19 (1.80)	$= 0.051$	0.15 (0.37)
Number of propranolol/nifedipine interventions per patient	2.0 (2.1)	< 0.05	0.62 (0.96)
Total number of circulatory interventions‡	41	< 0.05	14

Vasoactive hormones

Plasma concentrations of noradrenaline did not change significantly throughout the perioperative period in the clonidine group (fig. 1). Noradrenaline decreased during the infusion of clonidine ($P < 0.05$, postoperative stages compared with beginning of infusion). In contrast, the placebo group experienced a large increase in noradrenaline ($P < 0.001$ and $P < 0.01$ for perioperative and postoperative stages, respectively). This led to a large intergroup difference ($P < 0.05$ and $P < 0.001$ for the perioperative and postoperative periods, respectively). Adrenaline concentrations were greater in the placebo group ($P < 0.05$ for peri- and postoperative periods). However, the increase in adrenaline was not suppressed fully in the clonidine group ($P < 0.01$ between baseline and R6; no significant difference in the postoperative period). The vasopressin and renin concentrations measured in the clonidine group were 50% of those measured in the placebo group ($P < 0.05$ for AVP between groups; not significant for renin between groups). The mean plasma concentration of clonidine in the clonidine group was approximately 2 ng ml^{-1}.

Circulatory state

Heart rate decreased in the clonidine group ($P < 0.05$ and $P < 0.01$ in the clonidine group for the perioperative and postoperative periods, respectively) (fig. 2). Heart rate increased in the placebo group ($P < 0.01$ within the placebo group for the postoperative period; $P < 0.01$ between groups). Changes in MAP occurred in the opposite direction in the two groups when perioperative intervals are compared ($P < 0.05$). The changes in MAP observed after operation in the clonidine group were not significant. An increase in MAP was noted in the placebo group after operation ($P < 0.0001$); this difference between groups was not significant ($P = 0.058$). There were no significant differences in calculated systemic vascular resistances. The stroke volume increased in the postoperative period ($P < 0.05$) in the clonidine group and decreased in the placebo group ($P < 0.0001$ and < 0.05 for the peri- and postoperative periods, respectively), leading to an intergroup difference ($P < 0.01$). PCWP was

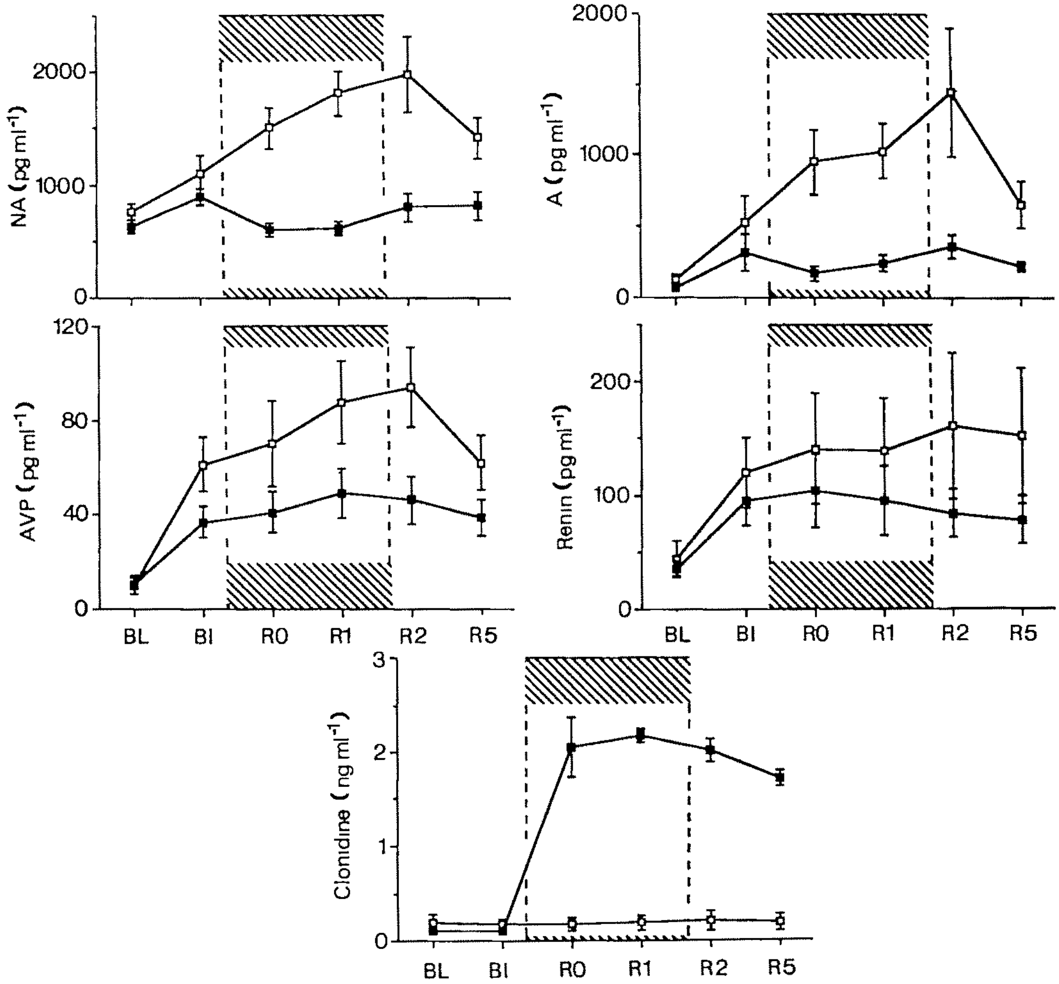

FIG. 1. Mean (SEM) plasma concentrations of vasoactive hormones during the postoperative period in patients who received placebo (□) ($n = 16$) or clonidine (■) ($n = 13$) infusion over 2 h (hatched area) after the end of aortic graft placement. The reduction in vasoactive hormone concentrations in the clonidine group achieved significance for noradrenaline (NA) ($P < 0.001$), adrenaline (A) ($P < 0.05$) and vasopressin (AVP) ($P < 0.05$) during the postoperative period. BL = baseline, immediately before induction; BI = before infusion; R0–R5 = sampling upon arrival in recovery room (R0) to 5 h after arrival in recovery (R5); renin = measurement of active plasma renin (ns between groups); clonidine = plasma concentrations of clonidine.

smaller in the clonidine group at baseline only ($P < 0.05$) (fig. 2).

DISCUSSION

Changes in concentrations of vasoactive hormones and cardiovascular variables in this study were similar to those reported during recovery from coronary [2, 4, 15, 16] or aortic [17, 18] surgery. As cardiac filling and systemic pressures and arterial blood-gas tensions were greater than baseline values or within the normal range, the surge in vasoactive hormones was not primarily a consequence of activation of baroreceptor (except immediately after administration of nifedipine) or chemoreceptor reflexes. This surge may be explained by incomplete postoperative central block despite the intraoperative use of a moderately high dose of fentanyl. This profile could also not be blunted by nifedipine/propranolol.

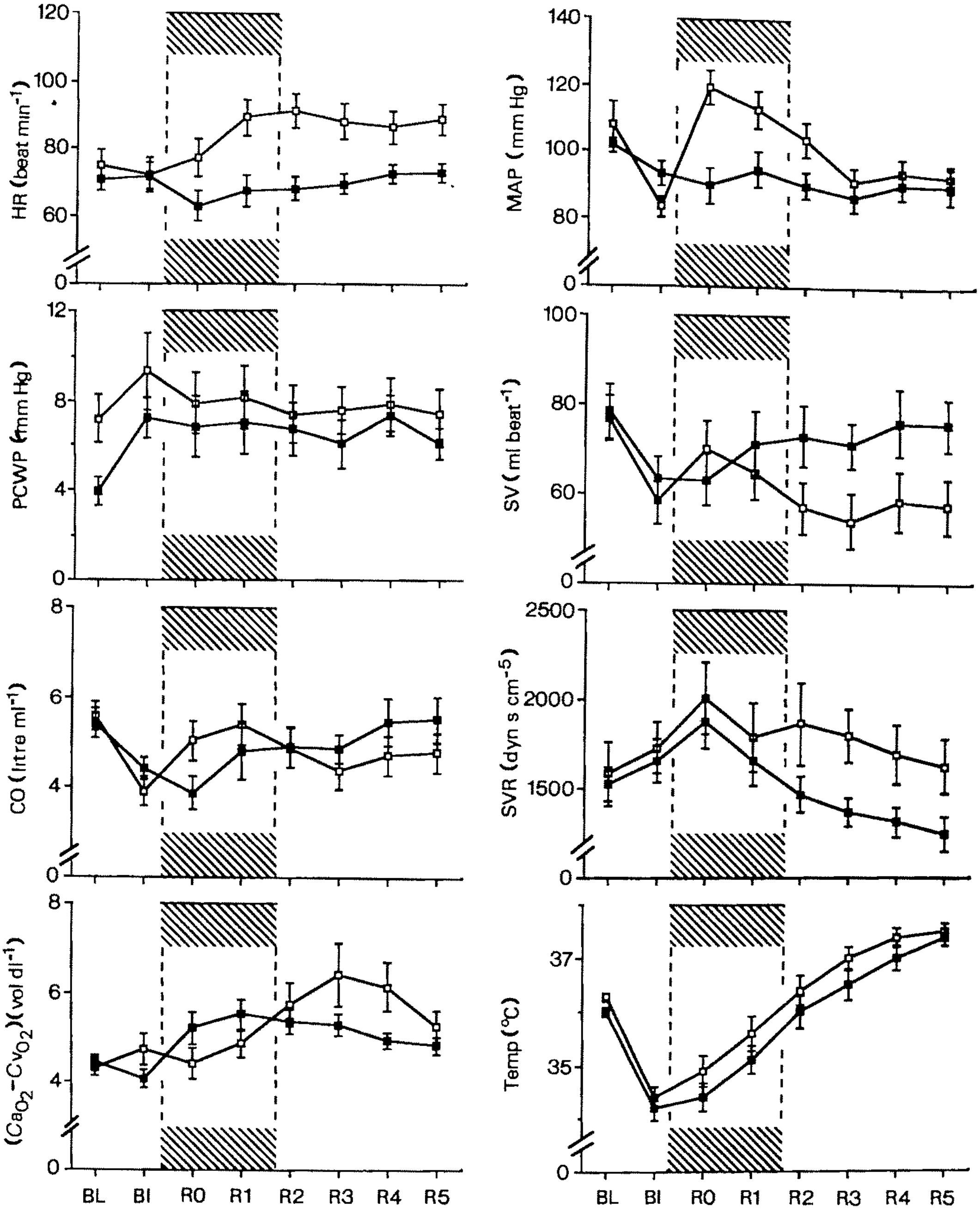

FIG. 2 Circulatory profile during the postoperative period in the placebo (□) and clonidine (■) groups (mean, SEM). Circulatory variables were measured hourly for 5 h after admittance to recovery room (R0–R5). HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; CO = cardiac output; SVR = calculated systemic vascular resistances; (Ca_{O_2}–Cv_{O_2}) = arteriovenous oxygen content difference; Temp. = core temperature; hatched area = infusion of placebo or clonidine.

The significance of this incomplete circulatory block and intact endocrine activation is unclear. Circulatory activation, especially tachycardia, is associated with increased coronary morbidity in the setting of coronary surgery [19]. Treatment with conventional therapy [20] or adrenergic inhibitors [21, 22], reduces mortality and the incidence of perioperative myocardial ischaemia. In contrast, providing the circulation is controlled, the hypothesis that endocrine activation is beneficial rather than harmful may also be considered. This opinion contrasts with the preliminary report that large plasma concentrations of catecholamines are associated with increased morbidity in the present [23] and other [24–26] circumstances.

The endocrine changes were modified substantially by clonidine, as reported previously for cortisol [27] and catecholamines [2, 4, 6, 7]. Whilst suppression of the adrenaline changes was not complete, noradrenaline concentrations were stable throughout the perioperative period. Given the limitations of plasma noradrenaline as an index of overall sympathetic activity, this observation suggests marked attenuation of hyperactivity. These findings are similar to those obtained after extradural morphine [18], except for the reduction of the vasopressin response seen in the present study.

Modification of vasopressin secretion observed in the clonidine group is in agreement with a previous report [9]. The reduction in AVP concentration is similar to that seen after high-dose opioids [28]. However, the possibility of highly selective manipulation of the central sympathetic–vasopressin integration [8] in the perioperative period, using a centrally-acting antihypertensive, is at variance [1, 8] with the use of anaesthetics [29] and opioids [28] for this purpose.

Extrapolation of the findings of our study suggests that the smaller changes in HR and MAP observed in the clonidine group combined with the larger stroke volume and lower calculated systemic vascular resistances at similar cardiac output, and the reduced incidence of shivering, might be helpful in reducing the extent of postoperative myocardial ischaemia. However, before considering clonidine as a possible adjunct to conventional postoperative management, several points should be considered. First, more poorly controlled hypertensive patients were included in the placebo group. Thus the difference in mean preoperative arterial pressure [30] could account for much of the difference in arterial pressure observed after operation. In a previous trial with treated hypertensive patients, there was poorer control of preoperative ambulatory arterial pressure and better postoperative control in a clonidine group [3]. Thus the unequal allocation of hypertensive patients is a flaw in this study, but it does not invalidate the findings of attenuation of the hormonal and circulatory responses. Second, clonidine may postpone hormonal activation beyond the first 6 h only. However, the dose of clonidine chosen is known to cause inhibition for at least 12 h beyond the period of study [Quintin, unpublished data]. Third, vasodilator therapy often induces a compensatory increase in vasoconstrictor endogenous compounds, such as angiotensin or thromboxane. An increase in angiotensin is unlikely, as concentrations of both renin and aldosterone are reduced by clonidine [10].

The effects of a high dose clonidine infusion on the cardiovascular system should be stressed. Cardiac output must be optimized before the infusion is commenced. The infusion rate should be controlled carefully as the tolerance of the cardiovascular system to clonidine is related inversely to its rate of administration [31]. Thus an abrupt reduction in sympathetic activity had to be avoided in view of the high concentration of catecholamines encountered before the infusion.

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CELLULAR MECHANISMS IN GENERAL ANAESTHESIA

G. POCOCK AND C. D. RICHARDS

The behaviour of an animal is governed by the activity of its nervous system and general anaesthetics are agents that disrupt behaviour. From this we may deduce that the principal target of general anaesthetics is the nervous system. To understand how anaesthetics work, however, we need to answer many questions:

(1) How do anaesthetics enter the nervous system?
(2) How are they distributed within the CNS and is their pattern of distribution fundamental to the generation of anaesthesia?
(3) Do anaesthetics act on particular nerve pathways or are their effects widespread?
(4) How do they affect the transfer of information between neurones—that is, how do they affect synaptic events?
(5) Do anaesthetics interfere with membrane-linked events such as ion channel behaviour and receptor properties or do they exert their effects via modulation of cellular energy metabolism?
(6) What is the nature of the interaction between anaesthetic molecules and their target site(s)?

As the functional unit of the nervous system is the neurone and as the overall pattern of nervous activity is governed by the functional connections between neurones (i.e. by synapses) the questions concerned with anaesthetic action on neuronal and synaptic activity are central to the discussion of the mechanism of anaesthesia. The issues raised by considering these questions form the basis of this review. The discussion of the other important issues is beyond the scope of this review, but the interested reader is referred to the articles in Papper and Kitz [72] and those by Mapleson [56] and Hull [40] for useful discussions of questions 1 and 2 and to the articles by Angel [3] and Richards [82] for discussion of question 3. Critical discussions of the molecular mechanisms of anaesthesia (question 6 above) may be found in the articles by Franks and Leib [28], Richards and colleagues [85] and Wann and Macdonald [108].

Before considering how anaesthetics act on neurones and synapses, it may be helpful to summarize the basic processes involved in synaptic transmission, which are potential sites of anaesthetic action (fig. 1). Impulses travelling in the presynaptic fibres invade the terminal branches to depolarize the nerve endings. This depolarization leads to the opening of voltage gated calcium channels and an influx of calcium into the terminal. The subsequent increase in intracellular calcium is the trigger for the secretion of transmitter substance from the nerve terminal by exocytosis. The released transmitter diffuses across the synaptic cleft and binds to specific receptor sites on the postsynaptic membrane. The result of this binding is a change in the permeability of the membrane to particular ions, which in turn leads to a change in membrane potential and so to excitation or inhibition, depending on the nature of the synapse. To determine how anaesthetics perturb synaptic mechanisms we shall investigate their action on each of the processes outlined above. In addition, it is necessary to determine if they also modulate the excitability of neurones by direct actions on the postsynaptic cell.

EFFECTS ON ACTION POTENTIAL PROPAGATION

Transmission through nervous pathways depends upon the propagation of action potentials along axons and on the transmission of information across synapses. Anaesthetic agents may exert their effects on one or both of these processes. In particular, local anaesthetics have been shown to block nerve impulse conduction by blocking

KEY WORDS
Theories of anaesthetic action.

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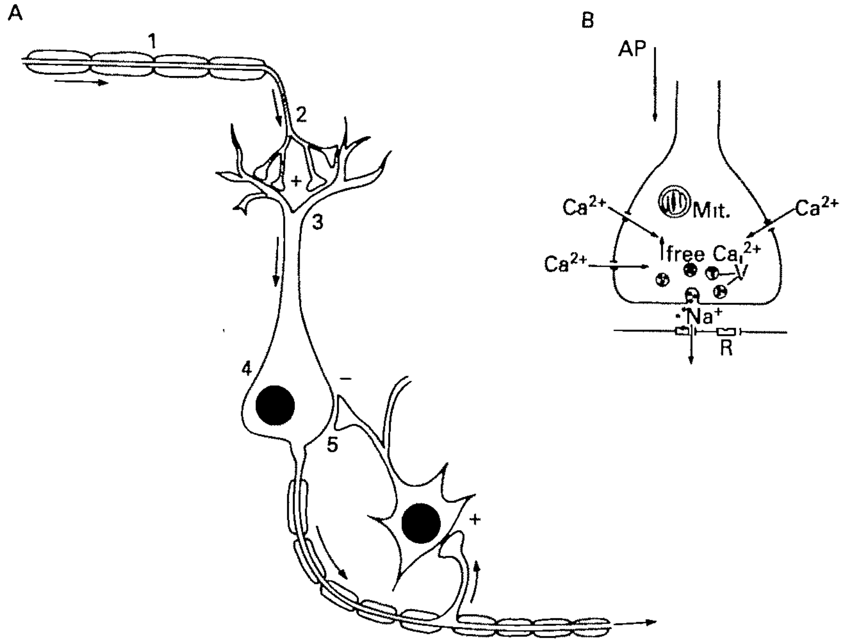

FIG. 1. Diagrammatic representation of the potential sites of anaesthetic action. A: A simple nerve network illustrating a typical neurone receiving excitatory synapses (+) on its dendritic tree and an inhibitory synapse (−) on its cell body from a recurrent inhibitory interneurone. Possible sites of general anaesthetic action are indicated by numbers: 1 = impulse conduction in presynaptic fibres; 2 = block of impulse transmission in fine nerve branches; 3 = block of excitatory synaptic transmission; 4 = modulation of the properties of the postsynaptic membrane; 5 = enhancement of inhibition. B: Enlarged view of a typical synapse to illustrate the fundamental mechanisms of synaptic transmission AP = Presynaptic action potential; Mit. = mitochondrion; R = postsynaptic receptor; V = synaptic vesicles containing transmitter (●).

voltage gated sodium channels [105]. General anaesthesia differs from regional anaesthesia in that it involves a loss of consciousness. This characteristic involvement of the higher functions of the nervous system was noted from the beginning and clearly has a different basis. In the early part of this century, Sowton and Sherrington [102] showed that chloroform blocked monosynaptic reflexes at much smaller concentrations than were required to block action potential propagation in motor nerves. This and subsequent work has led to the widely held view that general anaesthetics exert their characteristic effects by selective actions on synaptic events [4, 10, 17, 73, 79, 114]. However, in high concentrations, general anaesthetics may also produce action potential block. The possibility that this effect might contribute to the generation of the anaesthetic state has been suggested by Frank and Sanders [27] and by Seeman [95] and Staiman and Seeman [103].

This hypothesis is based on two pieces of evidence: the small diameter myelinated fibres of peripheral nerves are blocked more readily by both local [33, 63] and general anaesthetic agents [106] than are fibres of larger diameter; and local anaesthetics such as procaine may be used to supplement agents such as thiopentone to bring about general anaesthesia [27]. On the basis of this hypothesis, the mechanism by which general anaesthetics exert their effects would be as follows: they may impair impulse conduction in the fine terminal branches of afferent axons and, as the amplitude of the action potential invading the presynaptic terminals determines the amplitude of the postsynaptic potentials [43, 83], this reduction in action potential amplitude would lead inevitably to a reduction in synaptic transmission. Therefore this would be the fundamental mechanism by which general anaesthetic agents exert their effects. The idea is attractive, as it implies that local and general anaesthetic agents have a common mode of action via block of nerve impulse conduction. If this were true, the search for the molecular basis of anaesthesia would be greatly simplified.

This view has received fresh support from the work of Berg-Johnsen and Langmoen [11], who found that impulse conduction in small unmyelinated fibres (0.1–0.2 μm diameter) of the rat hippocampus was far more sensitive to block by isoflurane than impulse conduction in the myelinated fibres of the fimbria (1 μm diameter). While there is no doubt that general anaesthetics do reduce action potential propagation in nerve axons, the point at issue is whether or not this effect is principally responsible for depression of synaptic transmission which, in turn, leads to production of general anaesthesia.

The early studies of Bremer and Bonnet [15, 17] and of Larrabee and Posternak [47] amongst others [4, 18] showed that impulse conduction in axons was largely unaffected by a variety of anaesthetic agents at concentrations ordinarily required for surgical anaesthesia. Nevertheless, synaptic events were depressed significantly by concentrations of anaesthetics within the clinically relevant range. As Larrabee and Posternak have shown, however, these events were only some 5–10 times more sensitive to inhibition than impulse condution. Thus, in comparison with highly specific blockers of synaptic transmission such as atropine, tubocurarine or propranalol, anaesthetics are not very selective inhibitors of synaptic activity. More detailed work by Somjen [98], Somjen and Gill [99], Weakly [110] and Richards and co-workers [79, 81, 83, 86, 89] has confirmed that synaptic transmission in the CNS is significantly more sensitive to depression by general anaesthetic agents than is action potential propagation (fig. 2).

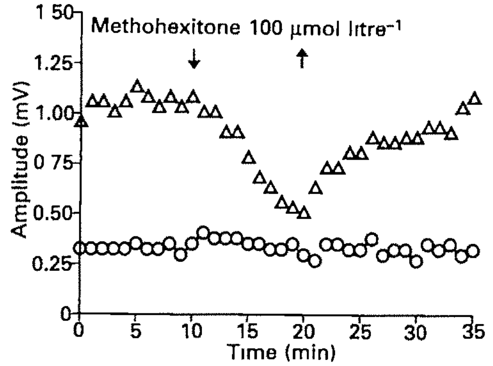

FIG. 2. Differential sensitivity to methohexitone of the presynaptic fibre action potential (○) and excitatory postsynaptic field potentials (EPSP) (△) recorded from the olfactory cortex of the guineapig *in vitro*.

If the effects of general anaesthetics on synaptic transmission are attributable to a failure of conduction in the presynaptic fibres, one would expect the decrease in amplitude of the synaptic potential to be accompanied by an increase in its latency. In addition, it should be possible to mimic the effects of general anaesthetics on synaptic activity by the local application of nerve blocking agents such as procaine or tetrodotoxin (TTX).

Detailed examination of the synaptic potentials evoked by electrical stimulation of afferent pathways in the olfactory cortex and hippocampus has shown, however, that a wide variety of general anaesthetics depress excitatory postsynaptic potentials (EPSP) with no significant change in their latency of onset [12, 71, 79, 81, 86, 89]. If, however, similar experiments are performed with nerve blocking agents, the latency of onset is increased as predicted [83]. Furthermore, when the amplitude of the action potential is reduced by progressive poisoning with the highly specific sodium channel blocker TTX, the reduction in the amplitude of the EPSP is proportional to the reduction in the action potential. In contrast, progressive increases in the concentrations of general anaesthetics produce a reduction in EPSP amplitude before there is any detectable effect on the action potential. In this regard, the action of general anaesthetics is selective for synaptic transmission. At high concentrations of anaesthetic such as those experienced briefly during induction of general anaesthesia, propagation of impulses may be impaired and this would clearly contribute to the depression of synaptic transmission. The extent of this additional effect would, however, be transient and would vary from agent to agent.

To summarize the evidence discussed above, it appears that general anaesthetics exert their characteristic effects principally at the level of the synapse and do not significantly perturb impulse conduction in nerve axons. As they depress excitatory synaptic transmission they must either decrease the release of transmitter from presynaptic nerve terminals or depress the sensitivity of the postsynaptic receptors to released transmitter, or both. The effects on inhibition are more varied, as both depression [10, 25, 30, 60, 96, 111, 113] and enhancement [25, 60, 64, 66, 67] of inhibition have been reported.

PRESYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

There is strong evidence that anaesthetics inhibit the secretion of neurotransmitter from nerve endings. The early work of Matthews and Quilliam [57] showed that several anaesthetics, including barbiturates, depressed the amount of acetylcholine released from sympathetic ganglia following electrical stimulation of the preganglionic nerves. Later studies of depolarization-induced transmitter release from brain tissue slices have shown that anaesthetics depress the secretion of excitatory amino acids [44, 59, 77]. In contrast, some authors have reported increases in the secretion of the inhibitory amino acid GABA [21, 77], although others have reported that GABA secretion is inhibited by barbiturates [42]. In intact brain tissue, the interpretation of such studies is, however, complicated by the fact that these amino acids are involved widely in cerebral metabolism.

If we accept that anaesthetics inhibit the release of neurotransmitter substances from nerve terminals, the underlying mechanisms remain to be established. It is unlikely that decreases in transmitter release may be attributed to alterations in the content of neurotransmitters within the nerve terminals, as the total content either remains unchanged (for example glutamate, aspartate and GABA [77]), or is increased as in the case of acetylcholine [24]. Nevertheless, Bangham and Mason [7] have suggested that anaesthetics might deplete vesicular transmitter stores by dissipating the proton gradient across their surface membrane. This, in turn, would lead to a reduction in the secretion of transmitter in response to nerve impulses. One would expect also to see an increase in passive leakage of transmitter, particularly from cells which have previously been rendered more permeable by electrical or chemical means. They further suggested that such a mechanism might apply to the chromaffin granules which are found, for example, in sympathetic nerve endings. The evidence for this view comes from studies of the effects of anaesthetics such as chloroform and diethyl ether which have been found to increase the permeability of liposomes to entrapped catecholamine. Bangham, Hill and Mason [6] have observed also that a reduction in extracellular pH inhibits the secretion of noradrenaline from splenic nerve terminals [78]. Akeson and Deamer [2], however, have shown that anaesthetics do not cause a major depletion of catecholamines from isolated chromaffin granules. Furthermore, Pocock and Richards [75, 76] have found that a variety of anaesthetics are without effect on the leakage of catecholamine from intact bovine chromaffin cells (fig. 3) or from those rendered leaky to small molecules by exposure to high voltage electrical discharge (electropermeabilization) (fig. 4). These experiments are discussed more fully later.

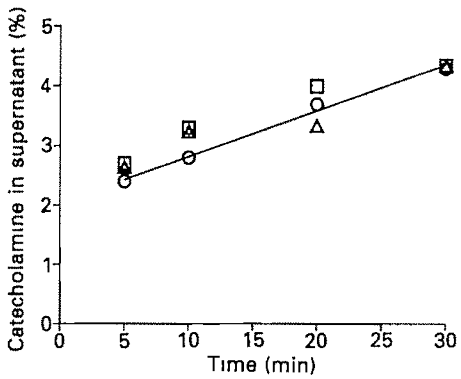

FIG. 3. Action of pentobarbitone 50 µmol litre^{-1} (△) and 200 µmol litre^{-1} (□) on spontaneous catecholamine release from freshly isolated intact bovine adrenal medullary cells (chromaffin cells). ○ = Control. Catecholamine secretion, expressed as a percentage of the total present in the cells at the start of the experiment, was unaffected by pentobarbitone. The regression line fitted to control data: $y = 0.07x+2.04$; $r = 0.99$

The weight of evidence, therefore, suggests that anaesthetics do not deplete presynaptic stores of transmitter.

Electrophysiological evidence that barbiturates cause a reduction in the release of neurotransmitters from central synapses comes from a study by Weakly [110], who found that low doses of thiopentone and pentobarbitone decreased the quantal content of EPSP in motor neurones without changing the amplitude of miniature EPSP. Halothane [115] and diethyl ether [114] have been reported to have a similar action. What are the underlying mechanisms for this effect?

Within the CNS it has proved difficult to assign specific transmitters to particular neural pathways accessible to experimental study. Simplification of this type is, however, an essential prerequisite for any detailed analysis of the action of anaesthetics on transmitter release. In addressing this problem,

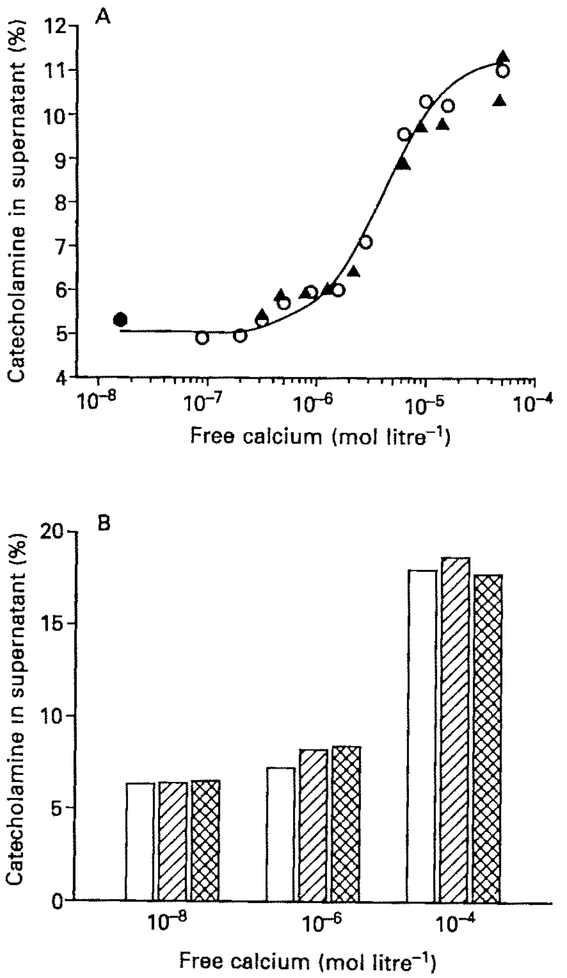

FIG. 4. Relationship between catecholamine secretion and free intracellular calcium in bovine chromaffin cells rendered permeable to small molecules by exposure to high voltage electrical discharge (electropermeabilized cells). Results are from individual representative experiments. A: Effect of pentobarbitone 200 μmol litre^{-1} (▲) on the calcium activation of secretion. ○ = Control. B: Effect of minaxalone 50 μmol litre^{-1} (☒) and methoxyflurane 900 μmol litre^{-1} (▨). ☐ = Control.

Pocock and Richards [75, 76] have investigated catecholamine secretion from isolated chromaffin cells. These cells offer a suitable experimental model, as their mechanisms of secretion of transmitter have been well characterized [5]. The cells are derived from embryonic neural crest tissue and are homologous with sympathetic postganglionic neurones. In response to acetylcholine released from splanchnic nerve terminals, chromaffin cells generate action potentials and secrete the catecholamines adrenaline and noradrenaline by calcium-dependent exocytosis. They also secrete catecholamines in response to direct depolarization by high concentrations of potassium. A wide variety of anaesthetic agents have been shown to depress the catecholamine secretion evoked by potassium both in intact adrenal glands [34, 35, 39] and in isolated cells [75, 76, 104] (fig. 5). In addition, all agents so far investigated decrease catecholamine secretion in response to acetylcholine or carbachol [34, 35, 39, 75, 76, 104] and in every case the sensitivity was greater than that of the response to depolarization with potassium (fig. 5). This indicated an additional, powerful effect of anaesthetics at the level of the nicotinic receptors. The implications of this finding will be discussed in the next section.

Anaesthetics could depress the transmitter secretion that occurs in response to depolarization by a direct effect on voltage gated calcium channels or on the intracellular events leading to exocytosis. To distinguish between these possibilities, Pocock and Richards [75, 76] examined the effects of pentobarbitone, minaxalone and methoxyflurane on the relationship between intracellular free calcium and catecholamine secretion using electropermeabilized chromaffin cells. Figure 4 shows that none of the anaesthetics affected this relationship. Moreover, the depression of potassium-evoked catecholamine secretion caused by most anaesthetic agents was paralleled by an inhibition of calcium influx (fig. 6). A similar depression of potassium-evoked calcium influx was reported by Blaustein and Ector [14] for rat brain synaptosomes exposed to anaesthetic concentrations of barbiturates. Some preliminary investigations suggest that volatile anaesthetics inhibit the increase in cytoplasmic free calcium caused by depolarization [45] and that barbiturates modulate the steady state cytosolic concentration of calcium [61]. In support of this, barbiturates have been found to decrease the voltage-dependent calcium conductance of cultured neurones [112]. Halothane [76] and ketamine [71, 104], however, have little depressant effect on potassium-evoked calcium influx or on neurosecretion.

It is now known that there are at least three types of voltage gated calcium channel—L, N and T [70]—and it is not yet clear which of these is the target for anaesthetic action. Direct depolarization by potassium would be expected to activate all

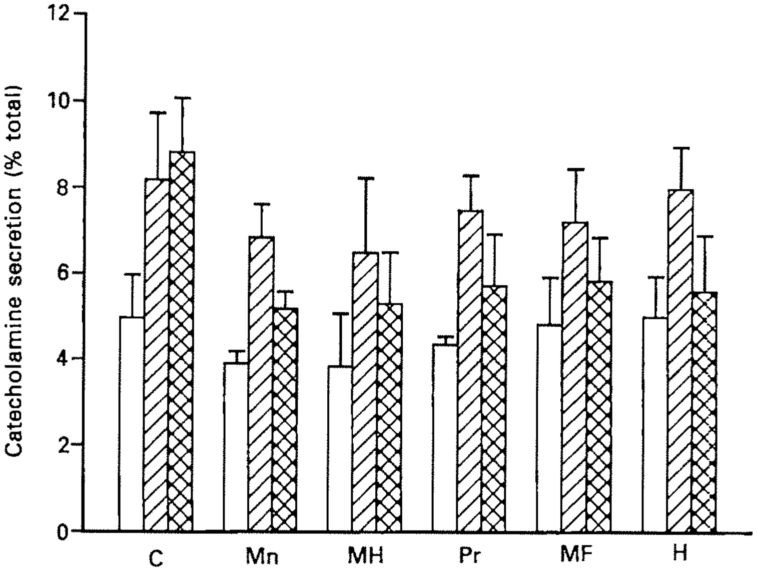

FIG. 5. Action of five anaesthetic agents on basal catecholamine secretion (□) and on that evoked by high concentrations of potassium (▨) and carbachol (☒). Cells were suspended in Locke's solution containing appropriate secretagogue and the amount of catecholamine appearing in the supernatant was measured after 10 min and expressed as percentage of total. C = Control (pooled data for all experiments); Mn = minaxalone 10 μmol litre^{-1}; MH = methohexitone 50 μmol litre^{-1}; Pr = procaine 40 μmol litre^{-1}; MF = methoxyflurane 400 μmol litre^{-1}; H = halothane 500 μmol litre^{-1}. Error bars indicate SD ($n = 28$ for control, 4–7 for individual anaesthetic agents).

three types but, as the L type inactivates more slowly than the other two, it would contribute most to the calcium fluxes measured by Pocock and Richards [75, 76]. From this evidence we conclude that most general anaesthetics inhibit depolarization-induced secretion of transmitters by inhibiting calcium influx through voltage gated calcium channels.

POSTSYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

Effects on postsynaptic receptor mechanisms

There are three possible mechanisms by which anaesthetics could inhibit ion movements through ligand operated channels: they could act to desensitize the receptor, thereby reducing the number of active channels; they could reduce the specific conductance of the channels; or they could reduce the time for which the channels are open. Any combination of the three is also possible. For convenience, we shall consider the actions of anaesthetics on excitatory and inhibitory mechanisms separately.

Excitatory mechanisms. As mentioned previously, anaesthetics exert a more powerful depressant effect on the catecholamine secretion evoked by nicotinic agonists than on that evoked by direct depolarization [34, 35, 39, 75, 76, 104]. This difference in sensitivity indicates that, in addition to their effects on the voltage gated calcium channel, anaesthetics have a direct action on the nicotinic receptor or on the processes associated with its activation.

There is some evidence from work on the nicotinic receptor of the Torpedo electroplax [16, 26, 38, 58] that some anaesthetics may desensitize the receptor to acetylcholine. For barbiturates, this appears to result from an increase in high affinity binding of acetycholine to the receptor, from which it is slow to dissociate. This has the effect of reducing the number of active receptors and so could contribute to the depression of excitatory synaptic transmission. At present, there is little information about the underlying mechanism of this effect or, indeed, how general such a mechanism may be.

Pocock and Richards [75, 76] have shown that pentobarbitone, halothane and methoxyflurane inhibit catecholamine secretion induced by carbachol in a non-competitive manner and that these and other anaesthetics also inhibit the influx of

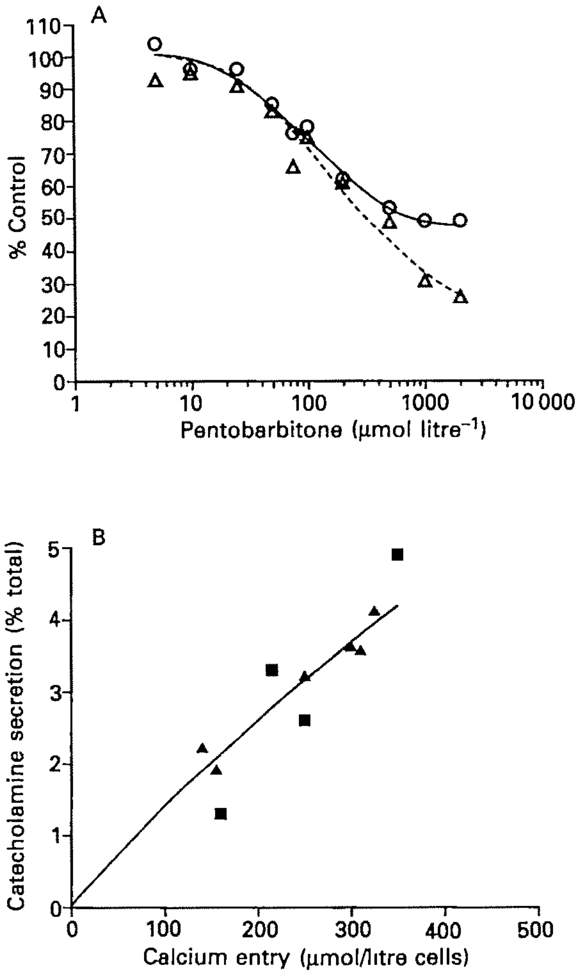

FIG. 6. Parallel inhibition by pentobarbitone of calcium-45 influx (△) and catecholamine secretion (○) evoked by potassium 70 mmol litre^{-1}. A: Dose–response relationship. B: Relationship between catecholamine secretion and calcium uptake evoked by stimulation with potassium. ■ = Relationship when external calcium was varied in the absence of pentobarbitone. ▲ = Relationship in cells exposed to varying concentrations of pentobarbitone in Locke's solution containing calcium 1 mmol litre^{-1}. The line was fitted by eye to the data for pentobarbitone and indicates that the inhibition of calcium influx by the anaesthetic is sufficient to account for the depression of evoked secretion of catecholamine (see [75, 76]).

both sodium and calcium ions evoked by carbachol. Whereas the inhibition of sodium influx could not account fully for the decrease in secretion, the inhibition of calcium influx paralleled closely the inhibition of catecholamine release. This contrasts with the failure of some agents such as halothane to inhibit either the catecholamine secretion or the calcium influx evoked by direct depolarization by high potassium and suggests that anaesthetics may inhibit calcium movements mediated by activation of the nicotinic receptor in addition to their effects on voltage gated calcium channels. It is, however, not yet clear which class of calcium channels is the target for anaesthetic action when chromaffin cells are stimulated by carbachol. Further work is needed to clarify the point.

Adams [1] has shown that, at the neuromuscular junction, barbiturates preferentially block ion channels in the open conformation, possibly by rendering this state less stable [31]. More recent patch-clamp studies on the nicotinic channels of adrenal chromaffin cells support this view, as pentobarbitone reduced the time for which the channels were open, but did not alter their specific conductance [41] (fig. 7). Similar findings have been reported for the action of ketamine on the nicotinic receptors of a tumour muscle cell line [107]. Acetylcholine receptors in the brain are predominantly muscarinic [46] and are thought to mediate slow synaptic excitation and inhibition by modulating potassium conductances [20, 36, 51, 52]. The effects of anaesthetics on this class of acetylcholine receptor have been studied by Smaje [97], who showed that volatile anaesthetics enhanced the response to iontophoretically applied acetylcholine, whereas alphaxalone depressed it. Pentobarbitone had no consistent effect on muscarinic excitation. Since this study was carried out, at least nine types of potassium channel have been shown to be involved in the regulation of excitability of central neurones (for a review see reference [37], and others in the same volume). There is at present very little information concerning the interaction of anaesthetics with these channels. Clearly, this is an important area for future study.

The amino acids aspartate and glutamate are thought to be important excitatory neurotransmitters in the CNS [97] and the action of anaesthetics on their receptors has received some attention. Early studies by Crawford [22] and Crawford and Curtis [23] showed that barbiturates reduced the sensitivity of neurones in the cerebral cortex to iontophoretically applied glutamate. Later studies confirmed this finding and showed that this was true also of other anaesthetic agents [86, 87]. These receptors were, however, resistant to depression by halothane at concentrations within the anaesthetic range [22, 87]. Since these studies were performed, the glutamate receptor

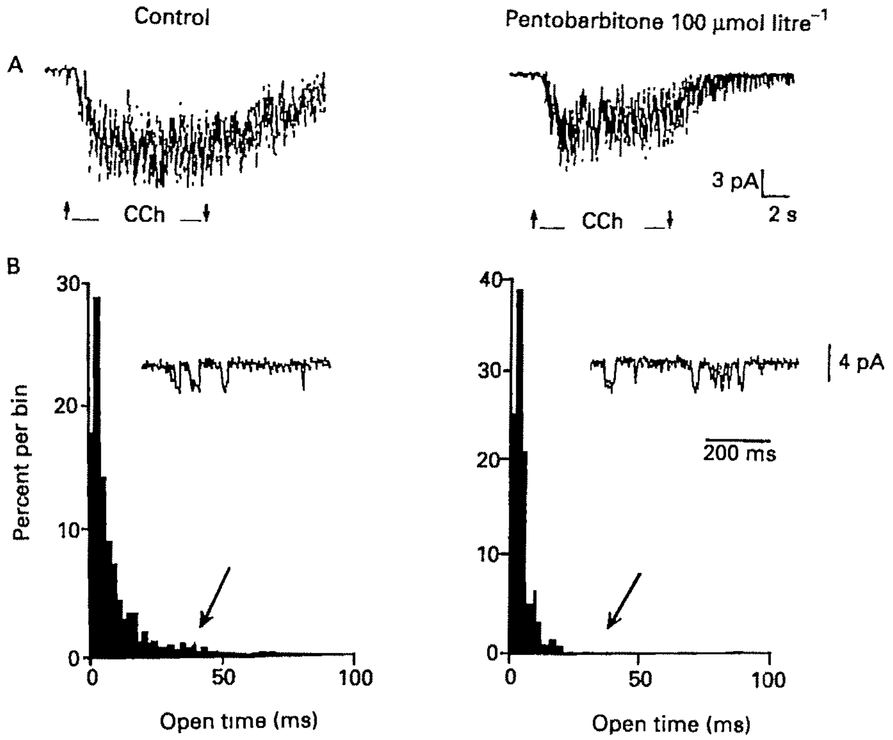

FIG. 7. Action of pentobarbitone on the behaviour of nicotinic ion channels in cultured bovine adrenal chromaffin cells. A: Reduction in carbachol (CCh) 10 μmol litre^{-1} -evoked inward current produced by pentobarbitone. B: Alteration in the pattern of channel activity produced by pentobarbitone. The inset shows carbachol-evoked channel openings in the presence and absence of pentobarbitone 500 μmol litre^{-1}. The main panels show the distribution of channel open times. Note the loss of channel openings of long duration (arrows) in the presence of anaesthetic. The records were obtained from single chromaffin cells by using the whole cell patch-clamp technique.

has been classified into three subtypes which have been named after their preferred agonists; N-methyl-D-aspartate (NMDA), kainate and quisqualate [109]. Ketamine and phencylidines have been shown preferentially to depress responses of the NMDA subclass [48–50], whereas pentobarbitone depresses the sensitivity of hippocampal neurones to all three agonists with quisqualate activation showing the greatest sensitivity [92]. The effects of other anaesthetics on the subtypes of the glutamate receptor have yet to be explored.

Inhibitory mechanisms. The actions of anaesthetics on inhibitory synaptic transmission are more complex than those on excitatory synaptic transmission. In general, barbiturates have been found to enhance both presynaptic [25] and postsynaptic inhibitory processes [32, 64, 66, 94], although other anaesthetics such as diethyl ether and isoflurane may have a depressant effect [10, 25]. Studies on brainstem neurones have described several responses to the action of general anaesthetics on inhibitory synaptic mechanisms [30, 96, 113]. Halothane predominantly depressed both excitation and inhibition, while barbiturates appeared to depress excitation but enhance inhibition [64, 66, 79, 89, 93, 96]. In spite of this apparent complexity, the cellular mechanisms that underlie both excitation and inhibition are essentially the same. The difference between excitatory and inhibitory synapses resides in the differing nature of their transmitters and in the characteristics of their postsynaptic receptors. It is probable that anaesthetics depress neurotransmitter release at both types of synapse and that enhancement of both presynaptic and postsynaptic inhibition may be attributed to interactions between anaesthetic agents and the postsynaptic receptor–channel complex (see below). The final result will depend upon the strength of the synaptic contact. For synapses with a low quantal content compared with the number of available postsynaptic receptors, the depressant action of anaesthetics on neurosecretion leads to depression of inhibition. In contrast, where synapses have a high quantal content, the action of anaesthetics on receptor-linked events is more important, and could lead to intensification of inhibition. Nevertheless, this issue is yet to be fully clarified.

In the CNS, the major inhibitory neurotransmitters are thought to be the amino acids GABA and glycine—GABA being the predominant inhibitory transmitter in the brain and glycine that in the spinal cord [46]. While little is known of the effects of anaesthetics on synapses utilizing glycine as a neurotransmitter, the action of anaesthetics on synapses thought to utilize GABA has received considerable attention. Pentobarbitone has been shown to prolong and intensify the hyperpolarizing action of GABA in frog motorneurones [65] and in mouse cortical neurones maintained in tissue culture [9], but did not alter the action of glycine [9]. Alphaxalone has been reported to have a similar action [8]. This hyperpolarization is probably the result of an increase in chloride conductance as a result of an increase in channel open time following activation [8, 9]. This increase in the effect of GABA is apparently not the result of either a decrease in its uptake or an increase in the affinity of the receptor for GABA [42]. Measurements of chloride currents activated by GABA in single chromaffin cells have supported this view [74] and have shown that alphaxalone has a similar action. This study also showed that barbiturates could directly activate chloride conductances in some cells, a finding confirmed recently by others [41]. In cultured hippocampal neurones and in dorsal root ganglion cells, enflurane has been shown to block slow responses to exogenously applied GABA whilst potentiating the rapid responses [19, 62].

Clearly, anaesthetics as a group affect profoundly the function of GABA-activated chloride conductances at concentrations within the clinical range. This suggests that the chloride channels represent a major target for anaesthetic molecules and the interactions between them require further investigation.

General anaesthetic actions on postsynaptic excitability

In principle, anaesthetics could modulate the electrical excitability of neurones in addition to the synaptic actions reported above. Early studies indicated that anaesthetics had little effect on the threshold for generation of action potentials [79, 81, 86, 88, 89, 99, 110, 114]. Moreover, in many cells general anaesthetics appear to have little effect on the ionic conductances of the resting membrane [9, 71, 88, 92, 100, 110, 114]. Several anaesthetics, however, including enflurane, halothane, isoflurane and ketamine [100, 101] appear to block accommodation in hippocampal neurones. The mechanisms that underlie this block may account for the reported increase in excitability of some neurones in the presence of isoflurane and enflurane [53, 60] and for the changes in firing pattern described by Fujiwara and colleagues [30] and earlier authors [54, 69, 80, 86, 91]. These effects on excitability are probably mediated, at least in part, by modulation of potassium channel activity [37, 100, 101]. In support of this, Franks and Leib [29] have shown that volatile anaesthetics inhibit the spontaneous firing of certain *Lymnaea* neurones by direct activation of a potassium conductance.

Direct effects of anaesthetics on the resting membrane potential have been reported by some workers [13, 68, 74] and have been ascribed to activation of specific conductances [74, 101], although other studies have found no evidence of such changes [88, 92, 99, 110, 114]. While the reasons for these differences are not clear, they indicate that changes in membrane potential are not a universal feature of anaesthetic action on CNS neurones. Nevertheless, small changes in membrane potential modulate the activity of low threshold voltage gated ion channels and this modulation, in turn, has important consequences for the pattern of neural activity. These observations, together with the effects on channel activity noted above, suggest a high degree of specificity in the interaction between anaesthetics and the ion channels which are their sites of action.

CONCLUSIONS

Although the mechanism of action of general anaesthetics has been studied at the cellular and subcellular levels, it is important to remember that, in the intact CNS, synapses operate within elaborate nerve networks. The overall effect of an anaesthetic agent, therefore, depends upon a summation of events occurring at many individual synapses. One would thus expect that the effects of anaesthetics on different neuronal pathways

TABLE I. *Effects of general anaesthetics on the processes underlying synaptic transmission. Effects summarized are those on synaptic activity in mammalian model systems at concentrations of anaesthetic sufficient to maintain general anaesthesia. For volatile anaesthetics, the minimum alveolar concentration (MAC) value has been taken as the standard anaesthetizing concentration. For i.v. agents, the values have been estimated from blood concentration. For further details, readers are referred to the original papers cited. †Data from unpublished work of the authors. 0 = No effect; ? = effect unknown; –?/+? = questionable effects; + = weak enhancement; + + = moderate enhancement; + + + = strong enhancement; — = weak inhibition; — — = moderate inhibition, — — — = strong inhibition. nACh = Nicotinic acetylcholine receptor; mACh = muscarinic acetylcholine receptor; ExcitAA = excitatory amino acid receptor; InhibAA = inhibitory amino acid receptor*

Anaesthetic	Action potential	Transmitter secretion	Effects on postsynaptic receptors: ExcitAA	InhibAA	nACh	mACh	References
Alphaxalone	0	— — —	— —	+ +	— — —	— — —	[8, 10, 84, 97]
Minaxalone	0	— —	?	+ +	— — —	?	Unpublished†
Methohexitone	0	— — —	— — —	?	— — —	?	Unpublished
Pentobarbitone	0	— — —	— — —	+ +	— — —	— —	[9, 25, 75, 79, 97, 110]
Thiopentone	0	— —	— — —	?	?	?	[23, 110]
Ether	0	— —	— — —	0	— — —	+ + +	[86, 87, 97, 114]
Enflurane	0	— —	?	?	— — —	?	[55, 76]
Halothane	0	–?	0	–	— — —	+ + +	[22, 81, 94, 97, 113]
Isoflurane	–?	— —	?	+	— — —	?	[11, 76, 95]
Methoxyflurane	0	— —	— — —	?	— — —	+ + +	[62, 76, 94, 97]
Trichloroethylene	0	?	— — —	?	?	+ + +	[80, 97]
Ketamine	0	–?	— — —	0	— — —	?	[32, 49, 71, 104]
Etomidate	0	— —	?	?	— — —	?	[90], Unpublished

depend upon the nature and activity of the ion channels within the cells comprising the network. Support for this conclusion may be drawn from the work of MacIver and Roth [55], who have shown that different anaesthetics exert different effects on the three principal pathways of the hippocampal formation.

Table I summarizes the effects of a wide variety of clinically important general anaesthetics on the events which underlie synaptic transmission. From the table it is evident that effects on impulse conduction in presynaptic fibres contribute little or nothing to the effects of most anaesthetics on synaptic activity. This is not surprising, as some anaesthetics, particularly the barbiturates, can both depress excitation and enhance inhibition. The data shown in the table further imply that, while general anaesthetics modulate the activity of presynaptic voltage gated calcium channels, the transmitter-operated ion channels in the postsynaptic membrane are more susceptible and may represent a major target site in the generation of anaesthesia.

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METOCLOPRAMIDE AND RENAL VASCULAR RESISTANCE

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SUMMARY

We have studied the effect of i.v. metoclopramide on renal vascular resistance in nine healthy volunteers. Peak systolic and end-diastolic frequencies were measured using duplex Doppler ultrasound of a renal interlobar artery, before and after the administration of i.v. metoclopramide 10 mg, and the resistance index derived. There was no significant change in mean arterial pressure or resistance index following metoclopramide.

KEY WORDS
Kidney · blood flow. Pharmacology metoclopramide.

The administration of low doses of dopamine results in preferential renal vasodilatation [1], an effect that is exploited in clinical practice both to prevent renal failure during high risk surgical procedures and to manage critically ill patients with oliguria [2]. Metoclopramide is a commonly prescribed antiemetic with central and peripheral dopaminergic antagonism [3]. A large, single 1–2.5 mg kg^{-1} dose of metoclopramide, used to prevent nausea in patients receiving chemotherapy, has been reported to reduce renal plasma flow [4]. However, the effects of a smaller, more commonly prescribed dose of metoclopramide (10 mg) on renal vasculature have not been reported in man. We have assessed renal vascular resistance following administration of i.v. metoclopramide using duplex Doppler ultrasound of a renal interlobar artery. The technique has been reported recently [5]; it is non-invasive, simple and rapid and provides instant results.

METHODS AND RESULTS

Nine healthy male volunteers, mean age 31.8 yr (range 28–37 yr), weight 82.3 (70–89) kg gave informed consent to participate in the study, which was approved by the District Ethics Committee. All subjects had refrained from alcohol- or caffeine-containing drinks for the previous 24 h and none had received non-steroidal anti-inflammatory drugs in the previous week. Plasma concentration of creatinine was normal in all volunteers. Subjects rested supine for 30 min, following which baseline measurements of heart rate, mean arterial pressure and resistance index were made. Metoclopramide 10 mg was administered i.v. and the measurements repeated 30 min later. Mean arterial pressure was measured using an automatic oscillometric recorder (Dinamap).

Peak systolic and end-diastolic frequencies were measured directly by the same investigator using duplex Doppler of an appropriate renal interlobar artery [5]. The lower pole of the right kidney (left kidney in one subject) was imaged from a posterolateral approach using a mechanical sector ultrasound scanner (ATL 600). Pulse Doppler velocity measurements were obtained by placing the Doppler sample volume in a superficial part of the lower pole and moving the sample volume in this area until a consistent signal was obtained. The Doppler signal was fed to a dedicated Doppler spectrum analyser (Doptek Ltd, Chichester, West Sussex) and the frequency spectra recorded. In each case, five cardiac cycles were evaluated before and after administration of metoclopramide. The resistance index was calculated as the difference between peak systolic

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TABLE I. *Mean arterial pressure (MAP) and resistance index (RI) before and after administration of metoclopramide (metocl.). An increase in RI reflects an increased resistance to blood flow*

	MAP		RI	
Subject No.	Before metocl.	After metocl.	Before metocl.	After metocl.
1	85	89	0.596	0.583
2	82	81	0.579	0.578
3	72	73	0.723	0.639
4	75	77	0.575	0.606
5	82	83	0.695	0.686
6	89	85	0.636	0.628
7	78	78	0.749	0.686
8	94	91	0.617	0.649
9	98	87	0.318	0.482
Mean	83.8	82.7	0.610	0.615
SD	8.6	6.0	0.126	0.063

and end-diastolic frequencies divided by the peak systolic frequency; no corrections are required in this calculation for variations in angulation between the ultrasonic beam and the artery being examined. Resistance index is accepted widely as a measure of the resistance to flow: the smaller the index the less the resistance.

Heart rate, mean arterial pressure and resistance index before and after administration of metoclopramide were compared using a paired Student's *t* test. There was no significant change after the administration of metoclopramide (table I).

COMMENT

The difference between our results and those reported previously [4] probably reflects the larger doses of metoclopramide used in the earlier study. The administration of low doses of metoclopramide results predominantly in dopaminergic D_2 receptor antagonism, but larger doses may result in D_1 receptor antagonism. Clinicians may be loath to prescribe a known dopaminergic antagonist to patients at risk of developing, or those with established renal impairment, for fear of reducing renal blood flow. These fears were not realized in the present study; the resistance index did not alter significantly after administration of metoclopramide, although we may have missed a transient immediate effect of the drug which is unlikely to be of any clinical significance. However, the effects of metoclopramide on renal vascular resistance in patients with renal impairement, or in critically ill patients already receiving low-dose dopamine infusions, may be different from those reported here and require further study.

The availability of duplex Doppler equipment in many hospitals allows analysis of changes in renal blood flow in the majority of patients. It is a technique which is relatively easy to learn. This study confirms the ease of measuring an index of renovascular resistance using duplex Doppler. As the technique derives an index for resistance to flow and does not measure absolute blood flow, it cannot be used for comparison between individuals. However, it remains a useful tool for documenting changes in renovascular resistance in individual patients.

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INTERPLEURAL REGIONAL ANALGESIA: DETECTION OF THE INTERPLEURAL SPACE BY SALINE INFUSION†

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SUMMARY

A saline infusion technique is described for insertion of an interpleural catheter, to reduce the incidence of pneumothorax during conduct of interpleural block, especially if the block is used as an adjunct to general anaesthesia.

KEY WORDS

Anaesthetic techniques, regional: interpleural block. Complications · pneumothorax

Reports of interpleural regional analgesia for pain relief after surgery [1–4] claim a low incidence of pneumothorax. A 16-gauge Tuohy needle is inserted percutaneously into the pleural cavity (the interpleural space); the end-point—penetration of the parietal pleura—is signalled by loss of resistance to air. By definition, the incidence of iatrogenic pneumothorax cannot be less than 100%.

The quantity of interpleural air (about 2–5 ml) may be harmless in the spontaneously breathing patient after operation. However, it may be less harmless if interpleural block is used to supplement general anaesthesia with nitrous oxide, as the gas would diffuse into the trapped air space [5], causing enlargement of the gas volume within the pleural cavity.

The saline infusion technique described is intended to reduce this risk.

METHODS AND RESULTS

Conduct of general anaesthesia

Twenty-four patients with normal chest radiographs undergoing cholecystectomy or mastectomy were premedicated with lorazepam 2.5 mg given 2 h before operation. After preoxygenation for 2 min, anaesthesia was induced with fentanyl 500 μg and propofol in a dose sufficient to abolish the eyelash reflex. Vecuronium 8.0 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with 70% nitrous oxide in oxygen and the lungs ventilated mechanically both in the anaesthetic room (Foomaster, M&IE) and in the operating theatre (Penlon 400 anaesthesia ventilator driving a circle system with a fresh gas flow of 3 litre min^{-1}). End-tidal carbon dioxide concentrations were maintained in the range 4.8–5.0% by means of a variable soda-lime bypass (Penlon). After surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg, combined with glycopyrronium 0.6 mg.

Monitoring during anaesthesia included airway pressure, pulse oximetry (Nellcor 100), automated oscillotonometry, mean respired concentrations of oxygen and nitrous oxide, capnography, neuromuscular block (Bard) and electrocardiography (Cardiocap, Datex).

Conduct of interpleural block

A 16-gauge Tuohy needle (Portex) with stilette removed was attached to a catheter sheath adaptor (Arrow). The adaptor, intended for the safe introduction of a flow-directed 7-French gauge catheter into a central vein, has a haemostasis flap valve with a Luer lock and side port (fig. 1). An infusion set charged with 0.9% saline was connected to the side port, the system flushed with saline to exclude air, and the infusion set clamped.

With the anaesthetized patient lying supine the Tuohy needle was inserted into the subcutaneous tissue overlying an intercostal space in the midaxillary line. The roller clamp was opened fully, but as a consequence of tissue resistance only a few

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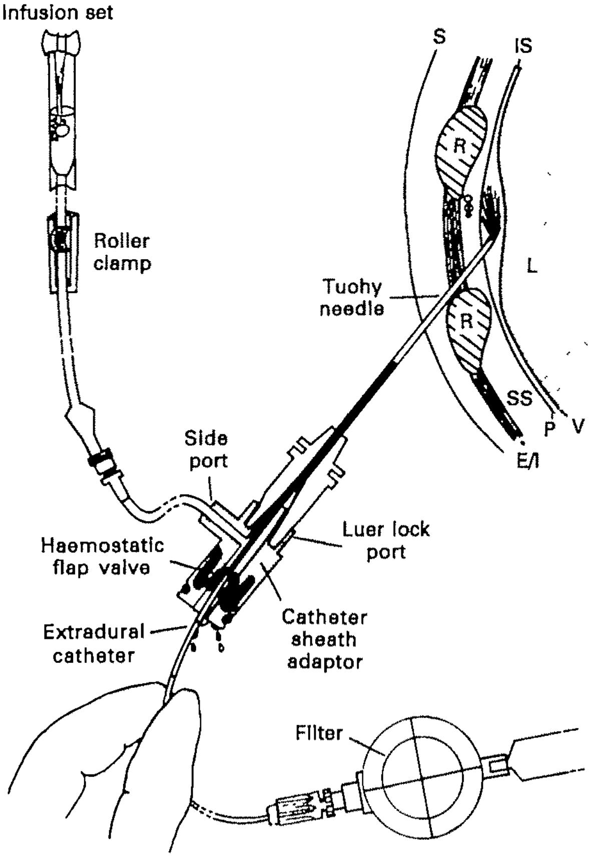

FIG. 1. Insertion of extradural catheter. Note: (a) continuous flow of saline from drip chamber into the interpleural space and leakage of saline from catheter sheath adaptor; (b) orientation of Tuohy needle. S = skin and subcutaneous tissue; IS = interpleural space; R = rib; L = lung; SS = subpleural space; E/I = external and internal intercostal muscles; P = parietal pleura; V = visceral pleura. The saline reservoir and the intercostales intimi muscles have been omitted for the sake of clarity.

drops of saline entered the drip chamber. Following 1 min of mechanical ventilation with 100% oxygen, the anaesthesia system was disconnected from the tracheal tube. During the period of disconnection (30–45 s) haemoglobin oxygen saturation was monitored by a second anaesthetist.

Closely observing the drip chamber, the anaesthetist advanced the Tuohy needle through the muscles of the intercostal space towards the parietal pleura. As the needle traversed the subpleural space a few drops of saline entered the chamber. When the parietal pleura was breached there was free flow of saline into the chamber and from thence into the pleural cavity. The absence of positive pressure in the lungs ensured that there was no limitation to lung recoil.

An extradural catheter (Portex, helical holes) primed with local anaesthetic and with a flat bacterial filter attached was passed through the flap valve of the adaptor for the desired distance into the pleural cavity. Saline leaked from the flap valve, thus preventing ingress of air (fig. 1). The Tuohy needle was withdrawn leaving the catheter *in situ*, the anaesthesia system reconnected and mechanical ventilation of the lungs resumed.

Following a negative aspiration test of the catheter, an appropriate dose of local anaesthetic was injected into the pleural cavity through the bacterial filter. The filter was disconnected temporarily to permit removal of the Tuohy needle and adaptor. The catheter was secured to the chest wall.

Studies in the awake patient

The technique was assessed in six awake spontaneously breathing patients with acute pain. The Tuohy needle was inserted under local anaesthesia during inspiration (but see Comment and reference [4]).

No anaesthetized patient developed pneumothorax during or after surgery as judged clinically, by intraoperative monitoring and by erect antero-posterior chest radiographs taken at end-expiration in the recovery room and 24 h later (cholecystectomy, $n = 21$; mastectomy, $n = 3$). There were no adverse effects attributable to the technique, and there was no evidence of awareness at any stage during anaesthesia.

There were also no adverse effects attributable to the technique in awake patients breathing spontaneously (multiple rib fractures, $n = 4$; pulmonary embolism with aseptic pleurisy, $n = 1$; recently performed intercostal nerve neurolysis, $n = 1$).

COMMENT

Pneumothorax is the most likely complication of percutaneous interpleural block induced at the termination of anaesthesia [1–4]; the gas space will contain nitrous oxide if the block is induced during anaesthesia. The saline infusion technique was devised to reduce these risks. Atmospheric air cannot enter the system. Puncture of visceral pleura or lung parenchyma with development of a tension pneumothorax containing nitrous oxide is unlikely, as the stream of saline appears to distance the visceral pleura from the parietal pleura. The end-point, penetration of the parietal pleura, is distinct.

Blocks were performed with the anaesthetized patient supine rather than in the customary lateral decubitus [1, 2]. Whatever the patient's anatomical position, local anaesthetic solution within the pleural cavity should flow according to the laws of physics: surface tension, gravity and gradients of interpleural pressure. However, it is still not clear how interpleural blocks act.

Saline infusion was successful in defining the interpleural space in the awake patient breathing spontaneously. It is debatable if the Tuohy needle should be inserted during inspiration, as in this study (the logic was to provide the most distinct end-point), or if it should be inserted during expiration [4].

Analgesia by percutaneous interpleural block appears to have been used mainly for pain relief after surgery. It is possible that the method may be used routinely before the start of surgery, in accordance with current views on mechanisms of pain [6]. If that happens, the reported incidence of pneumothorax may increase. The saline infusion technique described here may provide a wider margin of safety against pneumothorax than loss of resistance to air.

The catheter sheath adaptor is made by Arrow International Inc., Hill and George Avenues, Reading, Pennsylvania 19610 U.S.A., re-order No. SV-07000; British distributors Kimel Scientific Products Ltd, Unit E, Elkdale Road Trading Estate, Uxbridge, Middlesex UB8 2RT, U.K.

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ANAESTHETIC MANAGEMENT OF A 2-MONTH-OLD INFANT FOR LASER RESECTION OF VOCAL CORD GRANULOMA

S. L. TSUI, D. C. S. WOO AND J. R. LO

SUMMARY

A 2-month-old infant underwent excision of granulomata of vocal cords with a carbon dioxide laser. High frequency jet ventilation was given through a surgical metal suction tube during the operation. The anaesthetic technique for the infant and the problems of the use of carbon dioxide laser in laryngeal surgery are discussed.

KEY WORDS

Anaesthesia: paediatric. Surgery: laryngeal, laser. Ventilation, high frequency jet

The use of carbon dioxide laser in laryngeal surgery poses many problems in anaesthetic management. These include airway control, the necessity for adequate surgical exposure and immobility of target tissue. Various anaesthetic techniques have been described for laser surgery in adults and older children. In the present case report, the anaesthetic management of a 2-month-old infant undergoing laser excision of laryngeal granuloma is described and discussed.

CASE REPORT

A full term 1-month-old infant was admitted to our hospital with meningitis and respiratory failure: oxygen haemoglobin saturation (pulse oximetry) was 70%; the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) was 9.9 kPa. Convulsions developed and he was resuscitated successfully after tracheal intubation using a polyvinylchloride (PVC) tracheal tube, 3.5 mm internal diameter (i.d.) and mechanical ventilation. The meningitis was controlled after 1 week and he was weaned from the ventilator. However, several attempts at tracheal extubation during the following 2 weeks failed because of recurrent upper airway obstruction soon after the tracheal tube was removed. Direct laryngoscopy and bronchoscopy performed under general anaesthesia in the third week revealed multiple granulomata on both vocal cords. Excision of these granulomata with carbon dioxide laser was planned in the following week.

The infant presented for surgery at 2 months old (body weight 4.69 kg) with a 3.5-mm i.d. PVC nasotracheal tube *in situ*. Monitoring of this infant included continuous pulse oximetry (Ohmeda Biox 3700); transcutaneous carbon dioxide (Ptc_{CO_2}), electrocardiogram (ECG), rectal temperature (Kontron Supermon 7210) and arterial pressure (Critikon Dinamap Vital Sign Monitor 1846). The following items of apparatus were prepared: a paediatric microlaryngoscope (Storz) 11 cm long, i.d. 1.2 cm at its tip; a stainless steel suction tube (Storz No. 10381C) 30 cm long with i.d. and o.d. of 1.2 mm and 2.0 mm, respectively, having both end and side holes. The suction tube was marked with marking pen and a silk thread tied at 14 cm from its tip so that it protruded 3 cm beyond the microlaryngoscope.

The infant was premedicated with atropine 0.1 mg i.m. 30 min before operation. General anaesthesia was induced with isoflurane in nitrous oxide and oxygen using an Ayre's T-piece with Jackson–Rees modification. Atracurium 5 mg was given i.v. and ventilation was controlled manually. After positioning, the infant was given 2% isoflurane in oxygen for 3 min. The nasotracheal tube was then removed. The vocal cords were

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TABLE I. *Data on HFJV settings and monitored variables*

	Time after start of HFJV (min)					
	0	15	30	40	60	75
Ventilator settings						
Inspiratory oxygen (%)	0.35	0.35	0.35	0.35	0.35	0.35
Ventilatory frequency (b.p.m.)	400	400	250	250	250	250
Driving pressure (bar)	0.9	0.9	0.9	0.9	0.9	0.9
Inspiratory phase (% of cycle)	50	50	30	40	40	40
Measured inspiratory tidal volume (ml)	15	15	20	24	24	24
Monitored variables						
Sp_{O_2} (%)	100	100	94	100	100	100
Ptc_{CO_2} (kPa)	3.8	7.1	4.9	3.8	4.1	3.8
Arterial pressure (mm Hg)	88/60	140/90	100/66	130/85	110/80	90/60
Heart rate (beat min^{-1})	144	160	140	166	140	135
pH					7.429	
Pa_{O_2} (kPa)					34.09	
Pa_{CO_2} (kPa)					4.33	

exposed by the microlaryngoscope. The suction tube was then inserted into the trachea through the microlaryngoscope under direct vision to the depth marked by the silk thread. The silk thread was used also to stabilize the suction tube within the microlaryngoscope, and with this arrangement some degree of flexibility was allowed in case the surgeon needed to adjust the tube position for adequate exposure. High frequency jet ventilation (HFJV) was administered through the suction tube with an Acutronic 1000 ventilator via a Luer lock connection with the initial and subsequent settings as indicated in table I.

During HFJV, general anaesthesia was maintained with ketamine 10 mg i.v. followed by a continuous i.v. infusion of 5 mg h^{-1}. Supplementary i.v. 2.5-µg boluses of fentanyl were given (total dose 10 µg) when anaesthesia lightened. Intermittent i.v. doses of atracurium were given for maintenance of muscular relaxation.

During HFJV, development of hypercapnia was associated with hypertension and tachycardia. After adjustment of the frequency of ventilation and inspiratory phase, normocapnia was achieved but Sp_{O_2} decreased. Upon re-setting the inspiratory phase, optimal respiratory conditions were achieved. Subsquent hypertension and tachycardia were associated with the use of adrenaline 1:200000-soaked swabs by the surgeon for haemostasis.

The total duration of HFJV was 95 min and operating conditions were excellent. After completion of the procedure, 100% oxygen was administered by HFJV for 3 min and the metal suction tube was removed. A 3.5-mm i.d. Portex nasotracheal tube was inserted and secured. Residual neuromuscular block was antagonized with i.v. neostigmine and atropine. The infant resumed stable spontaneous ventilation through the nasotracheal tube. He was able to sustain an Sp_{O_2} of 93% while breathing room air 30 min after antagonism of the block. He was returned to the paediatric intensive care unit awake and alert.

Postoperative recovery was uneventful. There was no clinical evidence of barotrauma. Recurrence of vocal cord granuloma necessitated a total of four laser operations using a similar technique. Subsequent anaesthesia was smoother than the first time with the benefits of previous experience. The nasotracheal tube was not reinserted after the last operation.

DISCUSSION

Post-intubation vocal cord granuloma causing airway obstruction is uncommon in children [1]. The use of the carbon dioxide laser in laryngeal surgery is now well establshed [2], especially for excision of superficial soft tissue lesions [3]. It allows good haemostasis and is associated with minimal inflammatory reactions and oedema of surrounding tissues [4]. However, the use of the carbon dioxide laser does create many anaesthetic problems in laryngeal surgery.

Airway control. PVC or rubber tracheal tubes are flammable in oxygen concentrations as low as 25 % [5]. Several measures have been suggested to overcome this problem. First, non-flammable tubes such as metal (Norton) [6] or metallic-coated tubes (Xomed) may be used. Second, PVC or rubber tubes may be protected from the laser beam by wrapping with metal (aluminium or copper) foils or muslin [7], but this inevitably increases the diameter of the tube. Third, the larynx and tracheal tube may be packed with wet swabs [7, 8], although the swab becomes flammable if it becomes dry. Fourth, the tracheal tube can be removed intermittently during firing of the laser [9]. Finally, one can use jet ventilation via a non-flammable metal tube from above or below the vocal cords [10, 11].

Immobility of the target tissue. Movement of target may cause unintended injury to surrounding tissues [12]. Immobility may be achieved by using muscle relaxants [9] or maintaining spontaneous ventilation under deep general anaesthesia [13, 14].

Inhalation of smoke and debris. Smoke and debris are generated during laser firing to the larynx. Although the theoretical toxic effect and infective properties of the smoke and debris have not been sustained by either *in vitro* or *in vivo* studies [15], it is undesirable to insufflate them into the tracheobronchial tree.

Hazards to theatre personnel. In our case, the larynx was too small for a conventional metal or wrapped tracheal tube. Spontaneous ventilation was not possible because of significant airway obstruction and intermittent removal of the tracheal tube was impractical because multiple intubation and extubation inflict more injury on the larynx. More importantly, the time available for aiming and firing of the laser would be short in an apnoeic infant after extubation. Consequently, we decided to use a small metal tube for jet ventilation throughout the procedure because of the following advantages: the patient could be paralysed and his lungs ventilated without a tracheal tube or an air-tight seal [16]; the small size of the jet tube allowed adequate surgical exposure and escape of expiratory gas despite partial airway obstruction; the use of a metal tube avoided the danger of ignition inside the airway. The tip of the jet tube was positioned 3 cm beyond the tip of the paediatric microlaryngoscope so that it was located approximately 1 cm above the carina. Smoke and debris generated by the laser were evacuated by expiratory gas instead of propelled inwards by the jet. The use of HFJV in this infant had two additional advantages: because a much smaller tidal volume and smaller peak inspiratory pressure were used, less barotrauma was expected. Minute mucosal tears may be inflicted by the metal catheter tip or by a misdirected laser beam, and the jet of gas mixture in conventional jet ventilation may cause pneumomediastinum, pneumothorax [10] or pneumopericardium [17] with the high gas pressure and volume involved. The problem of excessive vocal cord vibration [10] in the gas current during conventional jet ventilation may be avoided as a smaller tidal volume is used with HFJV.

Initially, a tidal volume of $3\ \mathrm{ml\ kg^{-1}}$ was set and a ventilatory frequency of 400 b.p.m. was chosen empirically [18]. However, the initial $P\mathrm{tc}_{\mathrm{CO_2}}$ was high, although $Sp_{\mathrm{O_2}}$ was adequate. As the efficiency of carbon dioxide elimination is impaired when ventilatory frequency is increased beyond a certain optimal value [19–21], the ventilatory frequency was adjusted according to $P\mathrm{tc}_{\mathrm{CO_2}}$. The inspiratory phase was reduced in conjunction with the reduction in ventilatory frequency in an attempt to minimize vocal cord movement (smaller delivered tidal volume), but this was associated with a decrease in $Sp_{\mathrm{O_2}}$. After careful adjustment of ventilatory frequency and inspiratory phase according to $P\mathrm{tc}_{\mathrm{CO_2}}$ and $Sp_{\mathrm{O_2}}$, satisfactory gas exchange was eventually achieved. The disadvantage of HFJV is that the minute ventilation and tidal volume cannot be predicted or measured accurately [16]. Optimal gas exchange may be achieved only by close monitoring. The $P\mathrm{tc}_{\mathrm{CO_2}}$ (90 % response time in less than 60 s) is particularly valuable as it provides continuous information on elimination of carbon dioxide, and this correlates well with $Pa_{\mathrm{CO_2}}$.

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MUSCLE BIOPSY FOR DIAGNOSIS OF MALIGNANT HYPERTHERMIA SUSCEPTIBILITY IN TWO PATIENTS WITH SEVERE EXERCISE-INDUCED MYOLYSIS

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SUMMARY

Muscle biopsy and in vitro *contracture tests for diagnosis of susceptibility to malignant hyperthermia (MH) were performed in two patients who had developed fever and severe myolysis during exercise. MH susceptibility was confirmed in one patient, but in the other, exercise-induced heat stroke proved to be the correct diagnosis. Clinical presentation and epidemiology of exercise-induced MH and its relation to the heat stroke syndrome are discussed.*

KEY WORDS
Hyperthermia malignant

Malignant hyperthermia (MH) is a rare metabolic disorder presenting almost exclusively during anaesthesia. Apart from this classical appearance, a considerable number of MH episodes induced by either emotional or physical stress have been reported. Some of these case reports remain unproven, as MH was assumed or diagnosed by methods not generally accepted [1, 2]. In others, however, MH susceptibility was confirmed by *in vitro* muscle testing [3] in either the proband [4–6] or close relatives [5, 7].

Of 85 MH-like reactions reported to our unit between 1983 and 1989, 82 (96.5%) occurred during anaesthesia and only three (3.5%) during exercise. However, two of the latter patients were identified as carriers of the MH trait by *in vitro* muscle testing.

We present the case history of one of these MH-patients and compare it with that of another patient who had similar symptoms but was diagnosed as MH-negative (MHN) by *in vitro* muscle testing.

CASE REPORTS

Patient A

A 28-yr-old, well trained male took a physical test to qualify for a military unit. After 2 h of extensive exercising in an environmental temperature of approximately 21 °C, painful swelling of thigh muscles occurred. The patient felt extremely hot and "short of breath." Twenty-four hours later, generalized muscle pain was still present and his urine turned dark. The patient was admitted to the military medical department. He had fever (37.8 °C), a CK serum concentration of 64800 u litre^{-1} and serum concentration of LDH was 5880 u litre^{-1}. Other liver enzymes and coagulation screen remained within the normal range; blood count was not unusual apart from slight leucocytosis (15000 nl^{-1}). The diagnosis was heat stroke. No specific therapy was administered and the patient received i.v. infusions for 3 days. He recovered fully and was discharged 5 days after the event. An anaesthetist among the patient's circle of friends suspected a link between the above mentioned symptoms and MH trait and sent the patient to us. An *in vitro* contracture test confirmed MH susceptibility (MHS according to the European MH Group Protocol). The patient had had one uneventful

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anaesthetic for an appendicectomy at 12 years of age.

Patient B

A normally trained man, aged 26 yr, had the following symptoms during a mountain tour (military training in an environmental temperature of approximately 26 °C): after several hours on foot he felt dizzy and extremely hot. Several minutes later he lost consciousness and generalized muscle rigidity occurred. The helicopter rescue service was summoned and the patient was given diazepam, the trachea was intubated and controlled ventilation initiated. On arrival at the hospital he was still comatose, arterial pressure was not detectable and the heart rate was 210 beat min^{-1}. Metabolic acidosis was present (base excess -7.7, HCO_3 14 mmol litre^{-1}, Pa_{CO_2} 2.8 kPA, pH 7.40) and hypoxaemia was evident from a Pa_{O_2} of 5.8 kPa. Body temperature was 41.7 °C. Serum concentration of CK was 3358 u litre^{-1} and this increased to 45320 u litre^{-1} within a few hours. The patient received cooled infusions and after 3 h his temperature had decreased to 38.2 °C; arterial pressure was stable (110/70 mm Hg) and heart rate decreased to 120 beat min^{-1}. Myoglobinuria developed the next day. Renal function was preserved by infusion therapy. Severe coagulation defects and thrombocytopenia required administration of fresh frozen plasma and platelet concentrates. Gas exchange was now adequate with spontaneous ventilation. Subsequently, the patient recovered fully without any specific treatment and was discharged 6 days later.

In vitro testing was suggested by an anaesthetist; the test result was MHN, and thus confirmed the clinical diagnosis of exercise-induced heat stroke.

DISCUSSION

The case history of patient A clearly indicates the existence of the "human stress syndrome", confirming other authors' reports [4–7]. There is no doubt that exercise-induced symptoms as a primary manifestation of MH are much rarer than MH reactions triggered by anaesthesia. However, patients referred for muscle biopsy and *in vitro* testing are preselected by referring physicians. As anaesthetists have grown familiar with the symptoms of MH, adverse reactions during anaesthesia are reported immediately to specialized departments. In contrast, patients with exercise-induced signs are referred usually to other specialists unfamiliar with MH. Interestingly, probands A and B were referred to us by anaesthetists.

Epidemiological data from a group of patients in whom we performed muscle biopsies (table I) revealed that the frequency of exercise-induced symptoms (muscular cramps, pain and stiffness, and pyrexia) was greatest in MHS patients (nine of 86 = 10.4%). It was similar in MHE patients (8.5%), but was considerably smaller in the MHN group (1.8%). Although the difference was not statistically significant (MHS+MHE *vs* MHN: $0.05 < P < 0.1$), these findings support the results of Smith [8], who studied the personal histories of MHS, MHN and control patients and found that the presence of muscle cramps or weakness and intermittent fever were discriminating factors between the diagnostic groups.

The similarity between the case histories of

TABLE I. *Frequency and severity (number (%)) of exercise-induced symptoms in MHS, MHE and MHN patients. Data obtained from questionnaires completed by 311 patients before biopsy. † Patient A, present study; ‡ patient B, present study*

	Test results	Total frequency	Muscle pain	Muscle pain +pyrexia	Muscle pain −myolysis (myoglobinuria)
MHS	86 (100) (28)	9 (10.4) (53)	5 (5.8)	3 (3 5	1 (1.2)†
MHE	59 (100) (19)	5 (8.5) (29)	2 (3 4)	3 (5.1)	
MHN	166 (100) (53)	3 (1 8) (18)	2 (1.2)	0	1 (0.6)‡
Total	311 (100) (100)	17 (5 5) (100)	9 (2 9)	6 (1.9)	2 (0.6)

probands A and B suggest a possible link between MH and heat stroke [1, 4, 9–12]. In the so-called exercise form of heat stroke, muscles generate more heat than the body can dissipate, resulting in the symptoms reported in case report B. Heat production in MH is generated pathologically, but the outcome is the same in both cases. However, there is no clear evidence that MH patients are more liable to heat stroke than are normal individuals, nor is there clear evidence that heat stroke victims are liable to be MHS. This was established only in one case history [4]; the muscle biopsy required for the *in vitro* contracture test is obviously so invasive that large-scale clinical studies of heat stroke victims did not include tests for MH diagnosis [13].

In conclusion, MH susceptibility should be considered in patients reporting muscular pain, cramps or swelling, fever, or both, during or immediately after physical exercise. The same applies also to heat stroke victims.

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INTERHOSPITAL TRANSFER OF A PATIENT UNDERGOING EXTRACORPOREAL CARBON DIOXIDE REMOVAL

S. S. KEE, J. SEDGWICK AND A. BRISTOW

SUMMARY

Extracorporeal circulation techniques are being used increasingly in patients with acute cardiac or pulmonary failure. Some of these patients may subsequently require transportation, which has limited the use of these techniques in hospitals without on site transplantation facilities. We report a case of adult respiratory distress syndrome that demonstrates a solution to this problem.

KEY WORDS

Equipment. extracorporeal circulation techniques Lung. adult respiratory distress syndrome.

CASE REPORT

An 18-yr-old male was admitted to hospital following a road traffic accident in which he was the driver. Initially, his arterial pressure was 100/70 mm Hg with a sinus tachycardia of 180 beat min^{-1}. His ventilatory frequency was 30 b.p.m., with evidence of distress. There were bilateral basal crepitations and the initial chest x-ray was suggestive of pulmonary oedema. There had been a period of unconsciousness, but he was responding to his name and moving all limbs.

Facial examination revealed a mobile le Fort type III fracture with blood in the oropharynx. Orthopaedic examination showed avulsion of the superior pole of the left patella, rupture of the right posterior cruciate ligament and superficial lacerations. There was no radiological evidence of spinal injury. Peritoneal lavage was performed, with negative results.

Resuscitation with Gelofusin 1 litre and group O Rhesus negative blood 2 u produced a systolic arterial pressure of 200 mm Hg. Rapid deterioration in conscious level with evidence of pulmonary oedema necessitated urgent treatment. The trachea was intubated under barbiturate–relaxant anaesthesia and ventilation was controlled artificially.

Computed tomography revealed diffuse brain injury with no focal lesions and patent basal cisterns. A subdural intracranial pressure catheter was inserted and demonstrated a pressure of 5 mm Hg. The patient was admitted to the intensive care unit for further management. He remained hypoxic and hypercapnic despite ventilation with 100% oxygen (minute volume 12 litre; Pa_{O_2} 7.5 kPa, Pa_{CO_2} 6.8 kPa). His main problem was respiratory failure.

He was sedated and given anticonvulsant and H_2-antagonist therapy. The intracranial pressure was monitored and this remained normal for 3 days. The 12-lead ECG was normal. Enteral feeding continued to day five when bowel sounds disappeared, so parenteral nutrition was commenced. Although the patient was pyrexial, there was no bacterial evidence of infection at any stage, so the patient continued to receive cefotaxime and selective decontamination with gentamicin, amphoteracin and polymixin to prevent nosocomial pneumonia.

His second chest x-ray on the day of admission showed collapse of the right lower lobe, with overdistension of the left lung, therefore a bronchoscopy was performed, but this showed no

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evidence of aspiration or obstruction and that the major airway structures were intact.

The collapse was treated with asynchronous differential lung ventilation using a 41-gauge left-sided Bronchocath, and produced immediate haemodynamic improvement but no immediate improvement in respiratory function. Arterial blood-gas tensions were Pa_{O_2} 10.1 and Pa_{CO_2} 5.5 kPa, with pH 7.25 ($FI_{O_2} = 1.0$). The mean pulmonary artery wedge pressure was 14 mm Hg and the cardiac index 3.1 litre min^{-1} m^{-2}. Both oxygen delivery and oxygen consumption were within normal limits.

By the following day the right lower lobe had re-expanded and the respiratory function had improved, allowing conventional tracheal ventilation to be recommenced. However, left lung shadowing developed on chest x-ray and deteriorating pulmonary function necessitated pressure-controlled, inverse-ratio ventilation. This produced the best blood-gas tensions: Pa_{O_2} 14 kPa on 60 % oxygen. Over the subsequent 3 days, respiratory function deteriorated. Static lung compliance was 56 ml/cm H_2O and the clinical and radiological appearances were typical of adult respiratory distress syndrome. A trial of high frequency positive pressure ventilation (HFPPV) and cooling to a core temperature of 34 °C were unhelpful. Extracorporeal carbon dioxide removal with low frequency positive pressure ventilation ($ECCO_2R$–LFPPV) was commenced using femoro–femoral venous cannulation with a Biomedicus 540 extracorporeal pumping system and silicon membrane oxygenator with heat exchanger. The patient was heparinized to an activated clotting time of 200 s.

The initial blood flow through the extracorporeal circuit was 1.45 litre min^{-1} and there were no haemodynamic changes on commencing venous bypass with LFPPV and apnoeic oxygenation. Pa_{O_2} improved to 10.2 kPa, but two membrane oxygenators in series were required to reduce Pa_{CO_2} to 4.2 kPa.

The following 36 h were characterized by bilateral pneumothoraces. The ARDS worsened and it was decided that lung transplantation should be considered. The cardiothoracic team at Harefield Hospital were consulted and they requested that the patient be transferred.

Transfer by helicopter was deemed the most appropriate, as this provided substantially reduced transport times, a stable environment and the ability to power the $ECCO_2R$ system. Because the patient was critically ill, it was imperative that all monitoring was continued throughout the transfer. Careflight was able to provide portable monitors and equipment to replace the hospital's pulse oximeter, ECG, direct arterial and central venous pressures, core temperature, capnography and inflation pressures. Dopamine, dobutamine, heparin and blood infusions were maintained during transfer. The ventilator used during the journey was a portable gas driven, time cycled, rate set, pressure limited machine capable of delivering PEEP. Portable liquid oxygen cylinders were used to power and supply the ventilator and the $ECCO_2R$ system. Ordinary oxygen cylinders would have proved too heavy and bulky to use on the helicopter. The chest drains remained in place and presented no problems.

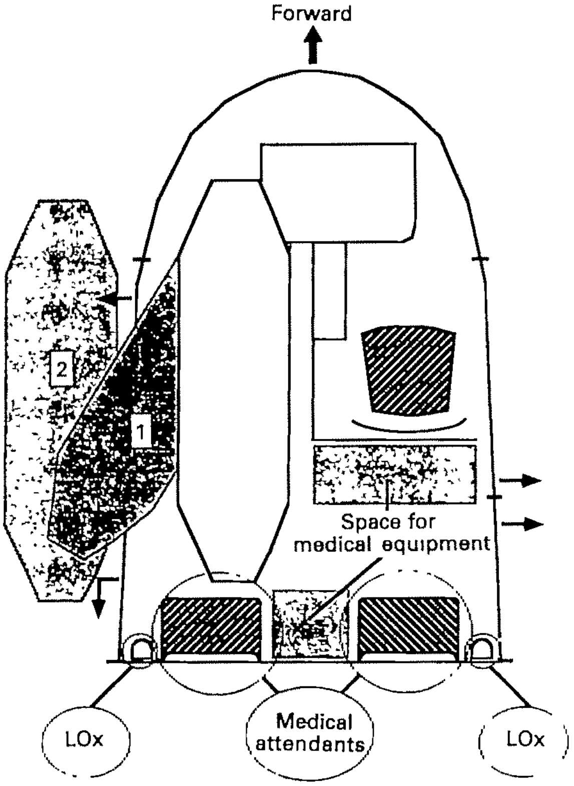

FIG. 1. Layout of helicopter ambulance: placement of patient, pilot and medical attendants. The anaesthetist was at the head of the patient. The position of the medical equipment, the sliding stretcher and the door exits are also shown. LOx = Liquid oxygen cylinder. (Reproduced by permission of Careflight and McAlpine Helicopters.)

The oxygen flow rate through the oxygenators was reduced to 15 litre min^{-1} to conserve oxygen use. The patient was attended by an anaesthetist and a perfusionist throughout the transfer. The patient was carried so that the body was parallel to the long axis of the aircraft and the head of the patient was placed aft to minimize haemodynamic shifts in blood volume caused by the helicopter's motion (fig. 1).

The 96-km journey took 30 min, during which time the patient remained stable. The heater on the $ECCO_2R$ system required 960 *W* necessitating 4 A at 240 V. The helicopter provided the power through a 28-V d.c. inverter to 240 V a.c. with a maximum current of 4.5 A. The monitors and infusion pumps drew 2.4 A, leaving 2.1 A for the perfusion equipment. This was sufficient to power the pump, but the reduction of 2.5 °C in core temperature was probably a reflection of the power limitation. Fortunately, the helipad at Harefield Hospital is adjacent to the hospital buildings, thus reducing the time of transfer between helicopter and hospital bed.

Thoracotomy after transfer failed to identify any specific bleeding sites. The patient remained critical but stable for 2 days, but no donor organs became available and death followed on the fourth day after transfer.

DISCUSSION

Extracorporeal membrane oxygenation (ECMO) is indicated for acute cardiac and respiratory failure not responding to conventional therapy [1]. The type of membrane support is determined by the method of vascular access, which may be venoarterial or venovenous. Venovenous ECMO provides gas exchange but no cardiac support [2]. The effects of embolization are fewer, and there may be a decrease in pulmonary hypertension because the oxygenated blood is distributed evenly throughout the pulmonary circulation [1–3]. However, venovenous ECMO is dependent on adequate cardiac function and compared with venoarterial bypass, venovenous bypass requires between 20% and 50% greater flow for total respiratory support because of recirculation of previously oxygenated blood [3–5].

Gattinoni and colleagues have demonstrated good survival outcomes in severe adult respiratory failure of parenchymal origin using LFPPV–$ECCO_2R$ [6]. The rationale with this method is to prevent further damage to diseased lungs by dissociating oxygen uptake and carbon dioxide removal. Oxygenation is accomplished primarily through the lungs by apnoeic oxygenation at a continuous positive pressure of 10–25 cm H_2O. Carbon dioxide removal is facilitated through the extracorporeal circuit. Three to five "sighs" per minute are required to preserve functional residual capacity. For the 51% of patients who did not wean from LFPPV–$ECCO_2R$, lung transplantation was the only viable alternative [6]. With the advent of percutaneous cardiopulmonary bypass as an emergency procedure, and an extension of the role of bypass to refractory myocardial infarction, massive pulmonary emboli and trauma cases [7], there is a need to transfer an increasing number of patients receiving extracorporeal support to cardiothoracic transplantation centres.

The major difficulty has been interhospital transfer. Land ambulances are generally not equipped with the power or monitoring equipment necessary to a mobile intensive care unit. A prospective study comparing helicopter and land ambulances demonstrated a significant reduction in predicted mortality of 25% in severely injured patients by use of the former mode of transport [8].

We are not aware of any patients receiving extracorporeal support being transferred in the U.K., and there is only one report from overseas, namely the transfer of a neonate with ECMO [9]. The helicopter not only overcomes the difficulties of land transfer, but also reduces the transit time significantly. This in turn allows ECMO and $ECCO_2R$ systems to be used throughout the country with the option of transplantation if the underlying pathology does not resolve. The development of such a system would be dependent on specialized transfer teams.

Transfer systems such as this also offer benefits for other critically ill patients. Work in California has emphasized that critically ill patients can be safely transported to tertiary centres if they are stabilized adequately and monitored carefully before and during transport [10]. The Clinical Shock Study Group at Glasgow has demonstrated that interhospital transfer of critically ill patients is safe with a dedicated specialized team of medical personnel and equipment [11].

Despite this, a recent questionnaire of general intensive care units in the United Kingdom revealed that 41% of respondents were dissatisfied with existing arrangements for secondary transport of patients [12].

St Bartholomew's Careflight is a dedicated secondary transport unit staffed by an immediate on-call medical, technical and aviation team.

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British Journal of Anaesthesia 1991; **66**: 145–147

CORRESPONDENCE

ANAESTHESIA FOR SIMULTANEOUS CAESAREAN SECTION AND CLIPPING OF INTRACEREBRAL ANEURYSM

Sir,—We wish to defend the use of extradural anaesthesia for Caesarean section in patients with intracerebral aneurysm. Recently we have managed a case similar to that described by Whitburn, Laishley and Jewkes [1] and used successfully an extradural technique for Caesarean section before proceeding to a craniotomy under anaesthesia with propofol and nitrous oxide.

The reason for avoiding an extradural technique is that an increase in extradural volume may cause an increase in intracranial pressure (ICP) and therefore compromise cerebral blood flow (CBF). However, this has been reported in only two patients [2], both of whom had sustained severe diffuse head injury. Furthermore, the increase in ICP was transient, and was appreciable in only one of these patients who was both comatose and had baseline intracranial hypertension. There was no evidence of increased ICP or decreased cerebral compliance either in our patient or in the patient reported by Whitburn, Laishley and Jewkes [1]. An editorial view [3] has concluded that a minor increase in ICP may be expected in normal individuals during extradural anaesthesia, which could be reduced by slower rates of injection.

Extradural bupivacaine provides excellent analgesia during surgery and in the postoperative period, permitting accurate assessment of conscious level. Furthermore, an extradural technique obviates the need to use general anaesthesia, tracheal intubation and β-blocker and vasodilator therapy, all of which have potentially deleterious effects upon CBF and ICP. Indeed, suxamethonium has been shown clearly in dogs and in humans to cause a significant increase in ICP [4, 5]. We suggest that, in common with extradural anaesthesia, the use of suxamethonium is controversial also in the presence of impaired cerebral perfusion, but each of these techniques has benefits which outweigh their risks.

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29-GAUGE SPINAL NEEDLES

Sir,—Having read with interest the reports by Dahl and his colleagues [1] on the technical considerations and incidence of postdural puncture headache (PDPH) using 29-gauge spinal needles in young patients, and by Haden, Scott and Pinnock [2] on the use of needles of the same gauge for spinal anaesthesia for Caesarean section, we should like to present some preliminary results of our own experience using 29-gauge needles for combined spinal–extradural anaesthesia for Caesarean section, with some thoughts on the future for such needles.

Comparison of the incidence of PDPH between different series is made difficult by failure to control factors which may affect the incidence, for example age, sex, gauge of needle and alignment of needle bevel. In addition, headache may be so transient that it may be difficult to establish if it is postural in nature. Consequently, we have found it more useful to establish the incidence of "significant" PDPH. This we define as any headache occurring after dural puncture which is not only postural but also is either (a) continuous for more than 24 h at any level of intensity or (b) so severe at any time that the patient is unable to maintain an upright posture; in other words, a headache which has any significant effect on the patient's postoperative well-being.

Using this definition, there has been no significant PDPH in our series, which so far consists of 163 patients. Several details of technique may have helped reduce this incidence. First, in almost all patients the spinal needle was inserted with the bevel parallel to the long axis of the vertebral canal (which has been shown to reduce the incidence of PDPH [3]). Second, the relatively oblique paramedian approach to the extradural (and consequently the subarachnoid) space was used in most patients, rather than the more perpendicular midline technique. It has been suggested that this may result in less leakage of cerebrospinal fluid through the dura mater after withdrawal of the needle [4]. The third factor is that almost all patients in this series received one or two injections of fentanyl made up to a volume of 10 ml with saline for postoperative pain relief. While it is difficult to see how the transient increase in extradural pressure produced by this technique could cause a lasting effect on dural leakage of CSF, extradural injection of larger boluses of saline has been recommended in the past as prophylaxis against PDPH [5].

Despite these possible criticisms, it appears from our results and those of others using 29-gauge spinal needles [1, 2, 6, 7] that significant PDPH with this gauge needle is almost nonexistent. This should make their use appropriate particularly in groups most susceptible to PDPH—obstetric patients and young patients undergoing day-case or other surgery after which they are quickly ambulant. Unfortunately, there are practical difficulties arising from the lack of "feel" with such fine needles and the long time to appearance of CSF at the metal hub after dural puncture, no needle manufacturer having yet succeeded in bonding transparent hubs to such fine needle shafts. As suggested by Haden, Scott and Pinnock [2], the use of the combined spinal–extradural technique tends to reduce these problems, the extradural needle guiding the fine spinal needle almost as far as the dura mater, but these difficulties are likely to limit their popularity for spinal anaesthesia.

One possible solution to both the manufacturing problems and the difficulties of technique with 29-gauge needles may be the use of larger needles with so-called "pencil-point" tips. Size for size, the original 20- and 22-gauge needles of this type [8, 9] were claimed to produce a lower incidence of PDPH than needles with conventional cutting tips. With improvements in manufacturing techniques, smaller gauge pencil-point needles are becoming available and it appears that, with these, the proportionally lower incidence of headaches may be maintained. Sprotte and colleagues [10], using a 24-gauge pencil-point needle for a variety of non-obstetric indications, and Cesarini and colleagues [11] using identical needles in obstetric patients reported exceptionally low incidences of PDPH—results confirmed in this unit in a pilot study using 26-gauge pencil-point needles for combined spinal–extradural anaesthesia for Caesarean section.

More evidence is required, but if these finer gauge pencil-point needles fulfil their promise, 29-gauge conventionally-tipped needles may become obsolete before they ever become popular—a fact unlikely to disappoint either manufacturers or anaesthetists.

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CHEST PHYSIOTHERAPY

Sir,—As a respiratory physiotherapist, I was most interested to read the article by Selsby and Jones on chest physiotherapy [1]. Whilst applauding any article which critically examines the practice of chest physiotherapy, I feel the following points merit attention.

Selsby and Jones, in common with many authors on this subject, refer frequently to postural drainage, percussion and vibration (PDPV) and discuss the merits of its use as a combined entity, without the clarification that PDPV actually involves three individual treatment techniques. Which, and to what extent each of these components may be effective remains doubtful [2] and further study of the individual manoeuvres is required before PDPV can be dispelled or accepted.

Second, in common with other medical and professional staff, the authors seem to be under the impression that chest physiotherapy must consist of PDPV or nothing. Although the forced expiratory technique is discussed, it is only one of many manoeuvres which lie between the extremes of PDPV and no chest physiotherapy. Techniques which utilize more physiological methods are often favoured [3].

Last, the article discusses physiological aspects of mucus clearance and refers frequently to sputum production. Whilst this is important, it should be remembered that this is not the sole aim of treatment, but part of an ultimate aim to improve ventilation and facilitate gas exchange.

Interestingly, the authors' reference list contains only two articles from physiotherapy journals, these being American in origin. Does this itself reflect the state of research into respiratory physiotherapy, particularly in this country? Selsby and Jones highlight some very relevant points for further study. Meanwhile, cautious application of findings of studies to date, and careful selective use of techniques by physiotherapists will provide patients with appropriate treatments and improve information on the usefulness of chest physiotherapy.

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Sir,—We thank Elizabeth Murray for her comments on our paper [1]. As stated in our introduction, because of the size of this subject we confined our review to some aspects of the problem, in particular those facets of chest physiotherapy that relate to mucus clearance. Postural drainage, percussion and vibration (PDPV), the forced expiratory technique and coughing exercises were discussed in detail because they are the techniques used most commonly for enhancing sputum clearance. PDVP was described as an entity as it was used in this form in almost all studies and it was not possible to evaluate the relative merits of each component.

We agree that additional therapies are used by physiotherapists in an effort to improve respiratory function. One of us has published extensively on the effects of gravity on regional lung ventilation, and this may be the basis of a further review relating to chest physiotherapy. We agree that further research into all aspects of chest physiotherapy is necessary both to avoid harmful techniques, and to ensure that patients with diverse respiratory problems receive the appropriate therapy.

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Sir,—I would like to comment on the review by Selsby and Jones [1] about the variations in the term and duration of chest physiotherapy (CPT) and the authors' coverage of hypoxaemia associated with CPT.

One of the difficulties of comparing the numerous studies on CPT is that the techniques used and termed by their users as CPT are different. As an example, reported treatment times range from 2–3 min [2], to 7–20 min [3], to a restricted predetermined duration of 10–15 min [4] or, as in our practice [5], CPT is continued provided secretions are still obtained, the patient is tolerant of the procedure and objective evidence is obtained of beneficial effect. The objective endpoints we use are increased air entry and reduction of adventitial sounds on clinical examination or increased total lung–thorax compliance (judged by a decrease in the end inspiratory pause pressure) of mechanically ventilated patients. Our treatment times quoted by Selsby and Jones (with their added exclamation marks) are inclusive of positioning for postural drainage and return to the original position at the end of CPT; positioning alone may take 10–20 min. Many studies of CPT do not use postural drainage [6, 7], other practitioners do not use manual chest vibration or percussion [7] and some do not encourage coughing [8] What is lacking in the literature is a definition of CPT. We have attempted to provide this [5]: CPT includes (a) positioning for postural drainage, (b) chest wall percussion, vibration or both, (c) coughing, (d) suctioning and (e) breathing exercises in the spontaneously breathing patient, including the forced expiration technique or huffing. It is not surprising that different results are obtained by investigators if different therapies are compared.

The second issue refers to the authors' lack of comment on postural changes as the cause of hypoxaemia after CPT. At least five reports [9–13] have shown that the prone position and dependent placement of the "good lung" can change oxygenation. In the studies quoted in which hypoxaemia occurred, lack of information about positioning of the patients or whether lung lesions were unilateral or bilateral, makes it difficult to exclude postural changes alone as the cause of the hypoxaemia.

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British Journal of Anaesthesia 1991; **66**: 148–150

BOOK REVIEWS

Intensive Care Manual, 3rd Edn. Edited by T. E. Oh. Published by Butterworths, London. Pp. 700; indexed; illustrated. Price £27.95

I looked forward with great interest to reading this book, as it is the third edition of a highly successful publication. It is a multi-author presentation, with virtually all of its authors originating from either Australia or Hong Kong.

Virtually the whole of intensive therapy is discussed, from staffing and administration through to the immunology of sepsis. Much of the material is presented clearly and logically. Each section is clearly subdivided and there are some diagrams There are useful appendices and the index is adequate.

The good features of the book are that it is very practical and where dogma is possible, firm recommendations are made. However, when subjects are discussed which are "difficult" (including for example septicaemia, ARDS, antibiotic recommendations and the use of sedatives in intensive care), the advice is not so clear cut but is, in many cases, vague. Although an attempt has been made to bring the references up to date, the principal reference quoted to the use of opioids dates from 1973, and the danger of accumulation of sedative drugs receives inadequate emphasis.

This is not a book for the curious because, in the majority of instances, statements are made without any attempt to give reasons or a physiological basis. Examples of this include: "An adequate haemoglobin level should be maintained". It is not stated what is adequate and why. In the section on epiglottitis, it is stated that "CPAP is useful during induction of anaesthesia. Care must be taken to avoid distending the stomach". How one is expected to do this is not explained. In the same section, after the correct observation that this condition is short lived, it is also stated that "tracheostomy is a satisfactory alternative (to intubation) depending on the availability of personnel". In the section on multiple trauma it is recommended, sensibly, that "oxygen therapy should be given to patients with fractured femur or more extensive injury because mild to moderate hypoxaemia are common". It is not stated why this is so.

There are many examples of similar frustrating statements and some with which the reviewer strongly disagrees. One example of this is the statement in the section on Acute Coronary Care, which otherwise is particularly good, that "pulmonary oedema responds to treatment with PEEP". In fact, all of the evidence implies that PEEP increases lung water. The final statement in the section on ARDS is that "most survivors have normal lung function although abnormalities in gas transfer persist".

There are many good points in this book. I believe that most of my criticisms stem from an attempt to make it fully comprehensive. There is no doubt that it would be useful to have a comprehensive text of a manageable size to recommend to both trainees and residents in an I.T.U. However, this book rather confirms the reviewer's personal opinion that such is not possible and that multiple monographs are required to fill this need.

J. C. Stoddart

Anesthesiology and Vascular Surgery: Perioperative Management of the Vascular Surgical Patient, 1st Edn. Edited by M. P. Yeager and D. D. Glass. Published (1990) by Appleton and Lange, East Newark, Connecticut. Pp. 395, indexed; illustrated. Price $69.95.

It is unfortunate that this book has a North American style of title and to read in the foreword that it is to a "limited degree" international in scope, for it is a very good book and the British, and indeed European, anaesthetist should not be deterred from reading it. Today we are experiencing a large increase in the number of patients presenting for major vascular surgery and we should not lose sight of the fact that most of the early work in this branch of surgery was carried out in North America. This book draws on this experience and it deserves international attention as it is comprehensive, contemporary and relevant.

Professors Yeager and Glass have drawn together successfully contributions from a total of 26 anaesthetists and surgeons from North America and Paris, France. The book is divided logically into five parts: Fundamentals; Preoperative Evaluation; Anesthesia and the Operation; The Postoperative Period and Anesthetic Practice in Evolution. These parts are divided further into a total of 15 chapters or contributions. The editors have succeeded in avoiding too much repetition and it is refreshing to find discussion of anaesthetic techniques and invasive monitoring with avoidance of dogma.

There is not a poor chapter in the book and each is well referenced, mostly from the North American literature, which is understandable. The chapters which stand out and should be of particular interest to all anaesthetists working in this field are: Surgical Technique and Judgement, Preoperative Evaluation, Monitoring Techniques, Infrarenal Aortic Surgery and Thoracic Aortic Surgery. The chapter on preoperative evaluation has been written by three authors from Paris and is comprehensive, particularly in its coverage of the assessment of cardiac function. The recommendation that coronary angiography is indicated in patients with an ejection fraction of less than 50% is perhaps controversial in the U.K., but financial constraints within the U.K. may be influential. The chapter on monitoring is an excellent review and it is refreshing to see the statement in a North American text that pulmonary artery catheterization is not recommended as routine in aortic surgery and should be reserved for those patients with severe pre-existing cardiac dysfunction. The chapter on thoracic aortic surgery from the Texas Heart Institute is recommended to all those embarking on anaesthesia for reconstructive surgery in these high risk patients. The immense experience gained in carotid endarterectomy surgery in North America is reviewed fully in two chapters entitled Cerebrovascular Surgery, and Prevention of Cerebral Ischemia. Happily, there is not too much overlap here.

The final section on Anesthetic Practice in Evolution contains chapters on optimal haemodynamic monitoring, prevention of cerebral ischaemia and regional anaesthesia for vascular surgery. These chapters are relevant to the practice of anaesthesia in patients undergoing any major surgery and are valuable reading. The chapter on regional anaesthesia written by Mark Yeager himself is a balanced discussion of the advantages and disadvantages of this technique in major vascular surgery. It is heartening to see postoperative pain control receive the prominence it deserves.

The only deficiencies in the book are inadequate coverage of anaesthesia for vascular access procedures for haemodialysis and anaesthesia in patients with renal artery stenosis and renovascular hypertension. The management of ruptured aortic aneurysm is covered, but the management of safe transfer of such patients from a peripheral hospital to a vascular surgery unit deserved consideration and, in particular, the role of military antishock trousers or the G. suit. There is only one drug, Benadryl, mentioned in the book which the British anaesthetist will not readily recognize. This is the only proprietary name used and it would not be our first choice as an antihistamine in any case.

The editors and contributors deserve credit for this text and all anaesthetists, spending an increasing amount of their time in vascular surgery, are recommended to read it.

J. H. McClure

Chest Physiotherapy in the Intensive Care Unit, 2nd Edn. By C. F. Mackenzie, P. C. Imle and N. Ciesla. Published by Williams & Wilkins, Baltimore. Pp. 387; indexed; illustrated.

The objective of this book is to provide a comprehensive reference source for physiotherapists involved in respiratory intensive care and to this end the authors make a special point that more than 900 papers are quoted. However, in the summary to the first chapter the reader is shaken to find that, despite this tidal wave of information, "objective studies of chest physiotherapy are few, the techniques employed are not standardised or adequately described, the patient populations are variable, sometimes inappropriately excluding those patients likely to benefit". So why collect such a mass of information when reliable studies are rare and the basic problems, the clearance of excessive airway mucus and the re-expansion of collapsed alveoli, are relatively few? The reader may expect the authors to provide a synthesis of this information to help to elucidate some of the problems of chest physiotherapy. In this regard most of Chapter 1, Controversies & Questions, was not reassuring. Paragraph followed paragraph with no obvious link. Each item in itself was of some interest but, in common with items in a jumble sale, there was no clear theme. However, the chapter concluded with a useful table which summarized many points of contention concerning chest physiotherapy, their advantages and disadvantages, and author's opinion. This was marred only by the omission of several references quoted in this table from the list at the end of the chapter.

The chapter on anatomy and physiology had nothing on respiratory muscle fatigue, airway mechanics in flow limitation and two phase flow. The last of these is the subject of a later chapter. The question of equal pressure point distribution, airway collapse and the effect of gravity on regional lung emptying at maximum flow was not discussed. An inordinate amount of space was allotted to gas exchange and was illustrated by some very old diagrams which are of dubious relevance to physiotherapists in the 1990s. A curious inclusion were two "diagrams" of lung sounds, one describing crackles and rhonchi in six languages (five European and Japanese!).

Subsequent chapters focus on the various methods used for postural drainage, percussion and vibration, methods of airway clearance, the physiological changes following chest physiotherapy, contraindications and the problems presented by special patients. All of these chapters are illustrated with numerous line diagrams and photographs. However, some of the latter are unclear and of dubious value.

Chest physiotherapy, particularly for patients in intensive care, is a very important part of treatment and much of this book is devoted to the practical procedures involved in the application of physiotherapy in these individuals. However, the book makes the point that many of the procedures have little or no scientific basis and they have not been subjected to clinical trials. There is now an impressive body of knowledge of lung physiology which is relevant to the work of physiotherapists in terms of both understanding the mechanisms of action of many procedures used by physiotherapists and studying their effect. It was disappointing to find that the opportunity of integrating this information had not been grasped fully.

In any future edition, the authors might be more selective in choosing the essential studies in the literature and aim for a book with more rigorous editing. In the meantime, this is a volume which contains much useful information and would be a useful addition to the departmental library.

J. G Jones

Textbook of Anaesthesia, 2nd Edn. Edited by A. R. Aitkenhead and G. Smith. Published (1990) by Churchill Livingstone, Edinburgh. Pp. 773; indexed; illustrated. Price £32.50.

When the second edition of this book arrived, two things were immediately apparent: the contributors had been drawn from a greater number of centres and the colours had changed. The cover of the first edition was red with yellow printing: the second edition still had yellow printing but the overall colour was bright green. Did the colour sequence of red, yellow then green mean that it was all go in this new edition?

In the early sections, basic science is discussed, with an excellent chapter on neurophysiology. However, in sequential chapters there is a difference of opinion as to how angiotensin II is produced, and some cardiac surgeons may not agree with the recommendations concerning anticoagulation in patients with artificial heart valves presenting for subsequent surgery.

The pharmacological section is fairly compact. However, with so much to learn, is there still a place for agents that are no longer manufactured? Is it not time that books, trainees and examiners left out these subjects by mutual agreement? There are very impressive chapters on local anaesthesia and techniques.

The chapters on basic physics and apparatus flowed one into the other, culminating in a well presented and clear account of the monitoring apparatus associated with anaesthesia. Again, is a chapter on operating theatre environment essential in a book designed primarily for tyros?

The chapters discussing everyday subjects such as E.N.T., ophthalmology and gynaecology are full of common sense. Further, they give very positive guidance in difficult managements, for example, the bleeding tonsil in a child. They are followed by chapters on day-case and emergency anaesthesia, with a good discussion on anaesthesia in odd situations.

The very important section on obstetric anaesthesia follows somewhat classical lines. However, not all anaesthetists would agree with the recommendations made for dealing with a failed intubation and perhaps a greater discussion is needed on this important subject.

The chapters on specialized anaesthesia are of excellent quality, very readable and certainly enough for the Part 1. Indeed, many could see a candidate safely through Part 3.

The reviews of the first edition were also available to the reviewer. How did the presentation of the second edition benefit from these earlier reviews? In general, the criticisms made had been rectified. However, the notable exceptions were the paragraphs on old disused drugs. Perhaps the third edition will also discard these items.

In summary, one can only paraphrase an earlier reviewer and say that "serendipity is, indeed a laudable characteristic of this formidable pair" They have succeeded in producing a very well presented book which was both educational and a pleasure to both read and review. Indeed then, the red, yellow and green sequence is mainly fulfilled, although occasionally the light may need a little polishing in parts. Not only would I recommend this book to all tyros, but I would also recommend it to departments and colleagues.

R. S. Vaughan

ABC of Transfusion, 1st Edn. Edited by M. Contreras. Published (1990) by British Medical Journal, London. Pp 66, indexed; illustrated. Price £10.95 in U.K., £13.00 abroad, including air postage.

This paperback is a compendium of 16 articles which appeared recently in the *British Medical Journal* and dealt with transfusion medicine. Taken together, they form a useful and digestible primer. With 21 authors in 16 chapters in only 62 pages of heavily illustrated text, there are variations in chapter quality and some repetition of illustrations and subject matter, occasionally within chapters. Laudable attempts to make the separate articles attractive to the general reader in the journal, with plentiful illustrations, work less well in the book format. For example, a colour illustration of a theatre scene with the legend "A number of operations do not require blood to be crossmatched", a colour illustration of six empty blood product plastic bags with the legend "Empty cryoprecipitate packs" and two illustrations of details of arterial surgery in a chapter on red cell substitutes might be deemed superfluous. The anaesthetist would be more interested in some chapters than in others—autologous transfusion is well covered, as are plasma, plasma products and indications for their use, and human albumin solutions. The support of the massively transfused patient would interest anaesthetists in training.

I would wish that this brief and helpful overview of the subject of blood procurement and transfusion practice might be read by all house staff and re-read by aspiring surgeons and anaesthetists, but it may not be so It will be useful, too, to nursing colleagues who work in clinical areas where blood usage is high, and to operating department assistants.

J. K Wood

Drugs and Anesthesia: Pharmacology for the Anesthesiologist. Edited by M. Wood and A. J. J. Wood. Published by Williams & Wilkins, London. Pp. 676; indexed; illustrated. Price £65.25.

This is the second edition of a standard pharmacology text book for anaesthesia, used extensively in the United States of America. As it is a purely pharmacological text, it can be used with equal effectiveness on both sides of the Atlantic.

In addition to those of the editors, there are contributions from nine other authors. The second edition retains the general format of the first, and has four sections: general pharmacological principles, drugs and anaesthesia, cardiovascular therapeutics and general therapeutics. In addition, there are useful appendixes describing paediatric dosages and pharmacokinetic parameters of some important drugs used in anaesthesia.

Without doubt, this book gives an excellent, up-to-date and comprehensive account of all drugs used in anaesthesia and is recommended very highly to all anaesthetists studying for examinations and those who need to refresh their memories.

It covers every aspect of standard pharmacology and also many new areas, for example pharmacology of 5-HT and prostaglandins. Each chapter is set out clearly in a logical fashion and is easy to read. The bibliographies at the end of each chapter are particularly good. There are many useful summary tables and diagrams which add substantially to the value of the text.

I have used this book on many occasions over the past few weeks as a reference text and have failed to find it lacking in any way It is a first-class book of exceptional quality and should find a place on every anaesthetist's book shelf.

D. J. Rowbotham

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

"KEEP A CLEAR AIRWAY"

One of the first skills that a trainee in anaesthesia is expected to acquire is the ability to maintain the anaesthetized patient's airway patent. The current concept of the mechanism of airway obstruction in patients who are comatose, anaesthetized or have received neuromuscular blocking agents, is that the tongue "falls back" and occludes the lower pharynx. Several well known textbooks contain diagrams that are artist's impressions illustrating this belief. Although this concept is supported commonly by reference to the classic radiological studies of paralysed patients carried out by Morikawa, Safar and DeCarlo [1], careful study of their report suggests otherwise. These authors showed that head tilt, with stretch of the structures between larynx and chin, was the most effective means of increasing hypopharyngeal patency. It is difficult to understand how this manoeuvre can "pull the tongue forward" to clear the airway. Everyday clinical experience emphasizes the relative unimportance of the action of gravity on the tongue in the development of airway obstruction, by the frequent need to maintain head extension, for example in patients lying on their side while recovering from anaesthesia, or in supine anaesthetized patients in whom an oral airway has been placed, which one might expect should overcome the problem of the tongue position. Using ultrasound to visualize the tongue, there seems to be little change in tongue position immediately after induction of anaesthesia with i.v. agents, although airway obstruction may supervene [2].

A recent upsurge in interest in the upper airway and the factors that regulate its patency has come from the recognition of sleep apnoea syndromes and the sudden infant death syndrome, both of which may be related to abnormalities in airway patency. How can we apply this information to improve our management of the anaesthetized patient's airway? Unfortunately, a great many of the data available are difficult to interpret and apply directly to the circumstances of anaesthesia. Techniques used commonly to study the airway are electromyography, measurement of pressure–flow relationships, and the method of acoustic reflection to assess airway area. In some circumstances, imaging by fibreoptic endoscopes, radiology, ultrasound, axial tomography or magnetic resonance has been used. Electromyography indicates muscle activity, but electrical activity does not necessarily indicate that the muscle is shortening, particularly in this region where so many muscles have almost opposing actions. The pressure–flow relationships in this region are complex, as the flow is often in transition from laminar to turbulent patterns, but it is possible to detect airway obstruction at different regions of the airway in normal human subjects during sleep [3]. Acoustic reflection is a promising and relatively non-invasive method that analyses reflections of a sound pulse projected down the airway [4]. The results agree reasonably well with those obtained by axial tomography, but the apparatus is unwieldy and requires the use of 80% helium to improve the resolution [5].

Although it appears that muscle activity may be a major factor in maintaining airway patency, it remains to be determined which of the many muscles are most important, and the main site or sites at which collapse occurs. The studies of Nandi and co-workers reported in this issue, [6], and those of others [3, 7], suggest that there may be more than one site. Investigation of this topic is complicated by the degree of reflex control of the activity of these muscles, and the possibility that some measuring devices may themselves influence the observations. For example, the use of a mouthpiece or similar apparatus alters breathing patterns and possibly muscle activation [8], and topical anaesthesia of the nose can cause abnormal breathing during sleep [9]. Although investigations with endoscopy may be possible in well anaesthetized patients, reflex responses may be exaggerated in circumstances such as barbiturate anaesthesia. Finally, the use of different forms of anaesthesia in many of the animal studies may be responsible for some of the contrasting results obtained [10].

Most human investigations have been of electrical activity of the genioglossus muscle, first studied by placing electrodes into the tongue either via the floor of the mouth or percutaneously [11], and later by surface electrodes placed either below the chin [12] or in a moulded mouthpiece [13]. Early reports were qualitative, but they suggested that there could be continuous activity of the tongue, particularly in its posterior part. Activity of the genioglossus was augmented during inspiration [11]. During rapid eye movement sleep, the activity became profoundly less, as does the activity in other skeletal muscles, and it was in this phase of sleep that obstructive apnoea was likely to occur. Airway patency was therefore attributed to activity of the tongue. It was argued that because activation of this muscle caused protrusion of the tongue, lack of activity would lead to a posterior movement. However, the mere association of loss of genioglossal activity with reduction of airway patency does not imply that the first event causes the second. Indeed, many muscles in the upper airway show an increase in activity during inspiration, such as the alae nasi [14], the tensor palatini [15], intrinsic laryngeal muscles such as posterior cricoarytenoid [16], and the strap muscles of the neck such as geniohyoid [17], sternohyoid, and sternothyroid [18]. As activity in many of the upper airway muscles changes in a similar way during ventilation it is possible that the activity of the tongue merely reflects changes in activity of the muscles that are more directly responsible for airway patency, rather than having an important effect itself.

Even in studies in which airway patency has been assessed before and after muscle activity has been abolished by nerve section, differentiation of the action of different muscles has not been established [17]. However, muscles that influence the position of the hyoid have been shown to influence airway patency. Stimulation of these muscles improves stability of the airway [18], and direct measurement of the length of these muscles shows that pharyngeal volume is increased as they shorten [19]. These studies in animals support observations in man during halothane anaesthesia, in which airway obstruction was attributed also to posterior movement of the epiglottis [20]. Relaxation of the neck strap muscles would cause such a movement. Obstruction may be overcome by extension of the head, to increase the passive tension in the muscles of the anterior neck, and so pull the hyoid forwards and with it the structures of the anterior pharyngeal wall, restoring airway patency—a mechanism recognized at least since the 18th century [21].

Is the activation of these muscles of the upper airway associated with actual dilatation of the pharynx? In animals anaesthetized with barbiturate there is evidence of upper airway dilatation during inspiration [22]. In addition to the effects of the neck muscles, however, the thoracic muscles may also influence the upper airway. During inspiration with the diaphragm, traction by the thorax on the strap muscles of the neck may increase airway size [23]. In conscious normal subjects, a reduction in lung volume by active exhalation from functional residual capacity to residual volume is associated with a reduction in area of the pharynx, by about 20% [24].

What factors influence activation of the airway muscles? Stimulation of ventilation by hypercapnia is associated with increased activity of the airway muscles [25], and lung volume-related reflexes that prolong inspiration also affect upper airway muscle action [26]. In addition, the upper airway is richly supplied with receptors that respond to pressure and flow [27] and a reduction in pressure in the upper airway such as might result from obstruction causes reflex activation of the tongue and neck strap muscles [28]. In normal human subjects, topical anaesthesia of the upper airway increases the incidence of episodes of airway obstruction during sleep, particularly if the pharynx is anaesthetized [29]. Hence, at least in some circumstances, upper airway reflex responses may contribute to airway patency. These different influences make it difficult, in the presence of partial or complete airway obstruction, to attribute increases in muscle activity to increased chemical drive, a reflex response to decreased pressure or flow in the airway, or a combination of these factors. In particular, studies of sleep apnoea patients may be difficult to interpret. Such patients have reduced pharyngeal size [24] and thus may have greater changes in upper airway pressure with ventilation, and hence reflex activation of the muscles of the airway, whereas normal subjects may not. Similar considerations could apply to older, male, and overweight patients who frequently have reduced airway dimensions [30] and are recognized by anaesthetists as having "difficult airways". In fact, during quiet breathing in normal subjects, genioglossus is relatively inactive and not always phasic [31], even in the supine position where airway size is reduced [32].

Anaesthesia or sedation often reduces respiratory drive, chemical responses and airway reflex activity, and it is not surprising that airway muscle activity is reduced. Although several studies have shown that increasing depth of anaesthesia causes a progressive reduction in upper airway motor activity [33, 34], there are few data comparing either the pattern or magnitude of activity in the conscious with the anaesthetized state. In awake cats with fine wire electrodes implanted in the tongue, tonic activity was more common than phasic activity [25], and in men with implanted electrodes, tonic activity was more common, although some phasic activity could be caused by maximal inspiration [Douglas, Warren and Drummond, unpublished observations]. Thiopentone causes a reduction in activity and a change in the pattern of activity from tonic to phasic [31]. As the reduction in activity of upper airway muscles seems to be greater than in the diaphragm, it is possible that the imbalance may predispose the upper airway to collapse [35], particularly if the onset of activity in airway muscles does not precede that in the diaphragm. Such a sequence of events has been demonstrated by the application of a hypoxic stimulus during sleep [36, 37].

Can we now add science to craft in airway maintenance? The changes in soft palate position observed by Nandi and co-workers [6] may be relevant: certainly, intranasal obstruction or reduced pressure at the nose can worsen airway obstruction during sleep [35, 38]. Exactly the same manoeuvres that help improve the airway in the anaesthetized patient also establish nasopharyngeal patency [39], and hence might reduce this tendency to airway occlusion. If the exact effects of airway maintenance manoeuvres can be estimated, then simpler and less invasive apparatus for airway management may be practical. The acoustic reflection technique may be useful for this because it permits frequent rapid measurements. Techniques such as nasal CPAP [40] or pharyngeal insufflation [41] should be investigated cautiously. Most important, simple formal clinical studies may be of value in defining the frequency, extent and factors associated with airway problems.

G. B. Drummond

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EFFECT OF GENERAL ANAESTHESIA ON THE PHARYNX

P. R. NANDI, C. H. CHARLESWORTH, S. J. TAYLOR, J. F. NUNN AND C. J. DORÉ

SUMMARY

Conventional lateral radiography was used in 18 elderly male patients to investigate the changes induced by general anaesthesia in the upper airway. The effect of tongue traction under anaesthesia was studied similarly in another 11 patients. Following induction of anaesthesia, there were highly significant approximations to the posterior pharyngeal wall of the soft palate (median change 1.3 mm, 95% confidence interval (CI) 0.3–2.6 mm; P = 0.006), tongue base (mean change 6.5 mm, 95% CI 5.3–7.7 mm; P < 0.001) and epiglottis (mean change 3.8 mm, 95% CI 3.1–4.5 mm; P < 0.001). Apparent radiographic occlusion of the airway occurred most consistently at the level of the soft palate (17 of 18 patients), sometimes at the level of the epiglottis (four patients), but the tongue base did not touch the posterior pharyngeal wall in any patient. Traction on the tongue failed to clear the nasopharyngeal obstruction. Attempted inspiration under anaesthesia caused major secondary collapse of the pharynx, with multiple sites of obstruction, similar to that found in obstructive sleep apnoea.

KEY WORDS

Airway. obstruction, pharynx, tongue. Anaesthesia general.

Obstruction of the upper airway under general anaesthesia has been recognized for more than a century, as has the effectiveness of head extension and anterior displacement of the mandible (the Esmarch–Heiberg manoeuvre) in clearing the airway [1]. Until recently this obstruction was attributed to posterior shift of the base of the tongue [2, 3], and it has been shown that both the normal phasic genioglossus electromyogram [4] and hypoglossal nerve activity [5] are depressed markedly during anaesthesia in the cat. The efficacy of the Esmarch–Heiberg manoeuvre also fits in well with this explanation of airway obstruction, as it displaces the insertion of genioglossus (and hence the tongue) anteriorly. The effect of anaesthesia seems to be paralleled by obstructive apnoea during sleep, when the genioglossus electromyogram may be depressed also during rapid eye movement (REM) sleep [6, 7].

However, more recent work in the anaesthetized human subject has challenged this view and implicated the epiglottis as a major cause of airway obstruction [8]. Our objective was to investigate anatomical changes in the pharynx during anaesthesia using a non-invasive technique in order to avoid distortion of pharyngeal structures by either mechanical displacement or reflex activity. We chose conventional lateral soft tissue radiography as providing the best compromise between practicability and fine discriminatory imaging of the air–tissue interface.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee, but restricted to male patients older than 60 yr (range 63–84 yr), presenting for routine urological procedures under general anaesthesia. All were in good general health with no symptoms suggestive of upper airway pathology or ob-

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This article is accompanied by an Editorial.

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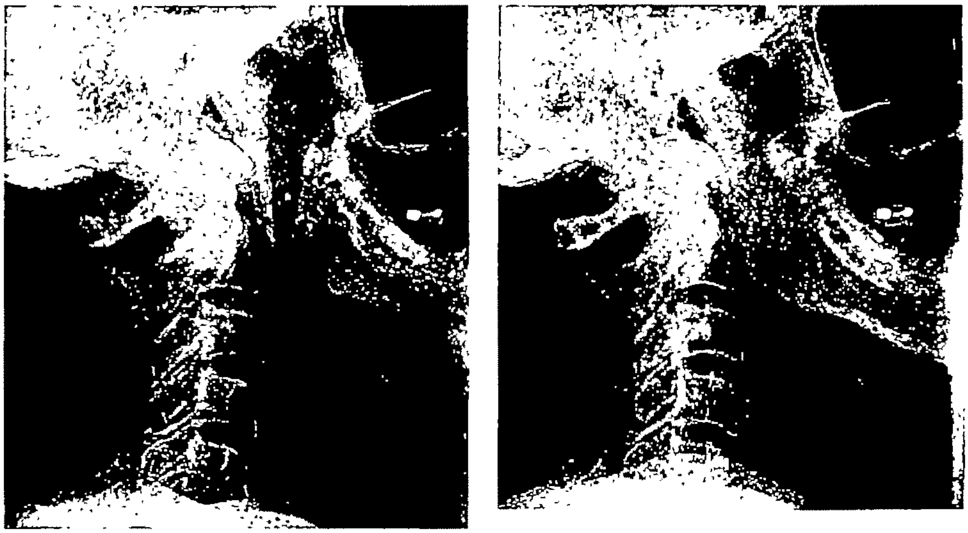

FIG. 1 Typical radiological appearances, before (left) and after (right) induction of anaesthesia.

structive sleep apnoea. Verbal consent was obtained on the day before the study. The majority of patients were unpremedicated, but four received i.m. papaveretum and one morphine 1 h before induction of anaesthesia, and three received oral temazepam 2 h before induction.

Eighteen patients were studied initially. Radiographs were taken in the anaesthetic room of the operating theatre, using a Dean 38 mobile x-ray unit (Dean GEC X-ray Operators Ltd, Wembley, U.K.). Exposure factors were in the range 62–65 kV (peak) and 12–16 mAs, depending on patient build. Exposure times were 60 ms. The focal film distance was 150 cm and the patient midline was 26 cm from the film. This produced a magnification factor of 17%, correction for which was made in the airway measurements. All radiographs were taken by the same radiographer (S.J.T.).

After insertion of an i.v. cannula, the subjects were instructed to breathe normally through the nose, with the mouth closed, while lying supine with the head resting on a ring support in a comfortably neutral position. The occiput was supported 3–5 cm above the plane of the table. A total of five radiographs were taken.

The first 10 patients were instructed to stop breathing for a few seconds at the end of a natural expiration while the first radiograph was taken, and at the end of a natural inspiration while the second radiograph was taken. The remaining eight patients were instructed to continue normal tidal breathing throughout, and radiographs were taken in mid-expiration and mid-inspiration as judged by motion of the epigastrium.

After the first two radiographs had been taken, anaesthesia was induced with thiopentone 3–5 mg/kg body weight and a third radiograph taken during the apnoeic pause. On re-establishment of spontaneous breathing, an oxygen–nitrous oxide–enflurane mixture was administered via a Magill attachment and conventional facemask. The inspired oxygen concentration was approximately 30%, and that of enflurane 3%. Head extension, with or without mandibular displacement, was required in all subjects to maintain airway patency after establishment of spontaneous breathing under anaesthesia; these manoeuvres were discontinued transiently and the head returned to the neutral position, in order to take the radiographs after re-establishment of spontaneous breathing at a light plane of surgical anaesthesia. For the first 10 patients these were at end-expiration and end-inspiration, and for the last eight patients in mid-expiration and mid-inspiration.

In another 11 patients (using the same criteria for inclusion in the study), both expiratory films were omitted, but an additional radiograph was taken under anaesthesia while firm traction was applied to the tip of the tongue using wide bore suction tubing to which a negative pressure of 200 mm Hg was applied.

Figure 1 depicts a pair of representative radiographs which illustrate the radiographic

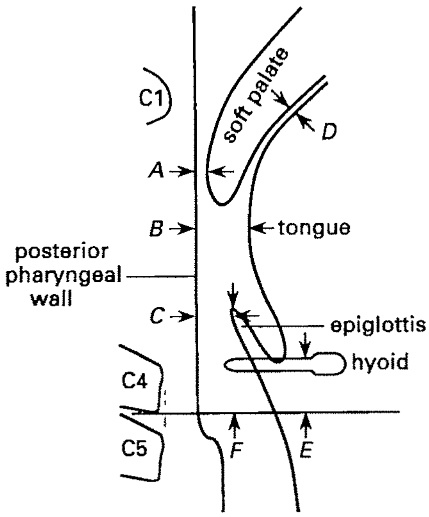

FIG. 2. Measurements made in each patient during the various stages of the study (see text and table I). Seventeen per cent was allowed for magnification in the x-ray.

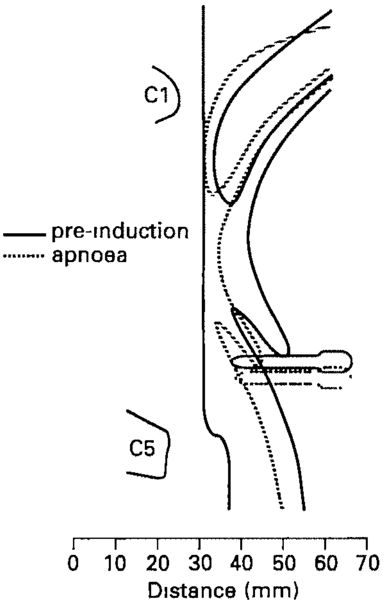

FIG. 3 Changes in pharyngeal outline immediately after induction of anaesthesia

anatomy of the peripharyngeal structures and demonstrate the typical changes which occurred after induction of anaesthesia.

Preliminary analysis of the radiographic findings consisted of making measurements of the width of the airspace in the sagittal plane at four standard sites (fig. 2):

A: the minimal distance from posterior pharyngeal wall to posterior aspect of soft palate;
B: the minimal distance from posterior pharyngeal wall to base of tongue;
C: the minimal distance from posterior pharyngeal wall to epiglottis;
D: the minimal distance from anterior aspect of soft palate to dorsum of tongue.

These measurements were made for all films; in the case of the pre-anaesthetic and apnoea films, two additional measurements were made:
E: the vertical height of the superior surface of the greater cornu of the hyoid bone above the lowest point of the body of the fourth cervical vertebra;
F: the vertical height of the tip of the epiglottis above the lowest point of the body of the fourth cervical vertebra.

In addition to these basic measurements, we constructed diagrams of a "mean airway" for each phase of the study (pre-induction expiratory, pre-induction inspiratory, apnoea, post-induction expiratory and post-induction inspiratory). Tracings were made of the outline of the pharynx and hyoid bone from transilluminated films, using as reference bony landmarks the anteriormost point of the body of the first cervical vertebra, and a line passing from it through the mid point of the anterior border of the fifth cervical vertebra. From these tracings, mean airway diagrams were drawn by superimposing tracings of individual patients' films on a single sheet, on which the visually estimated mean outline was then drawn manually. Validation of the accuracy of these diagrams was tested by comparing the means of the direct measurements *A*, *B*, *C* and *D* with the corresponding measurements on the mean diagrams; there was agreement in all cases to within 1 mm.

Statistical analysis of the six standard measurements was by paired Student's *t* test and two-way analysis of variance as appropriate, except in the case of measurement *A*, for which the data distribution was markedly non-Gaussian even after log transformation. In this case analysis was by the Wilcoxon matched pairs signed rank test.

RESULTS

Before induction of anaesthesia there were no significant phasic changes in sagittal airway configuration between either end or mid phase of breathing; this is the subject of a separate publication.

TABLE I. *Anaesthesia (apnoea) vs awake control and attempted inspiration during anaesthesia. Measurements are as shown in figure 2. Geometric means and their 95% confidence intervals (in parentheses) based on the pooled estimate of the within-subject variability obtained from the analysis of variance. *Median and 95% confidence interval for the median. †Wilcoxon's matched pairs signed rank test*

Measurement (mm)	Awake	Anaesthesia		P *vs* apnoea	
		Apnoea	Inspiration	Awake	Inspiration
A*	1.3 (0.3–2.6)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.006†	0.9†
B	9.6 (6.8–13.2)	3.0 (2.0–4.4)	1.2 (0.7–2.0)	0.001	0.006
C	5.5 (3.8–7.5)	1.8 1.1–2.6)	0.5 (0.2–1.0)	0.001	0.002
D	1.0 (0.5–1.6)	0.9 (0.4–1.5)	0.4 (0.1–0.9)	0.8	0.13

Apnoeic phase following induction of anaesthesia (fig. 3)

Following induction of anaesthesia, there were highly significant posterior displacements of the soft palate, base of tongue and epiglottis (table I). The displacement of the palate (median change 1.3 mm, 95% confidence interval (CI) 0.3–2.6 mm) resulted in apparent airway occlusion in all but one subject; that of the epiglottis (mean change 3.8 mm, 95% CI 3.1–4.5 mm) in only four subjects; and that of the tongue (mean change 6.5 mm, 95% CI 5.3–7.7 mm) in no subject. There was no significant change in the gap between posterior surface of tongue and soft palate. In addition, there were significant ($P < 0.05$) caudad shifts of both the epiglottis (mean change 3.8 mm, 95% CI 0.5–7.0 mm) and the hyoid bone (mean change 3.4 mm, 95% CI 0.02–6.7 mm).

Expiratory phase during anaesthesia

After spontaneous breathing under anaesthesia was established, there was a barely significant anterior movement of the epiglottis during expiration, but the other measurements were not significantly different from those during the apnoeic phase.

Inspiratory phase during anaesthesia (fig. 4)

After the re-establishment of spontaneous breathing during surgical anaesthesia, an attempted inspiration with the head in neutral position and the jaw unsupported resulted in extensive collapse of the pharynx, with significant reductions in most of its dimensions (table I). The tongue touched the posterior pharyngeal wall in seven, and the epiglottis in 10 of 18 patients.

Effect of tongue traction (fig. 5)

In the second series of 11 subjects, tongue traction was used to establish if the posterior shift in the soft palate was passively related to posterior displacement of the tongue. However, while tongue traction was highly effective in drawing the tongue base anteriorly, it had no demonstrable effect on the soft palate.

DISCUSSION

We are aware of only three studies [2, 9, 10] that have used conventional radiography to assess changes in pharyngeal configuration and airway patency in the anaesthetized, non-paralysed patient. Two of these involved very small numbers of subjects; none attempted any quantification of changes in anatomical dimensions.

In our study the primary and almost universal change was a posterior movement of the soft palate, which gave the radiological appearance of occlusion of the nasopharynx in 17 of 18 patients. Morikawa, Safar and DeCarlo [3] reported a mean posterior movement of the soft palate of 2.6 mm with occlusion in five of 10 patients following induction of anaesthesia and paralysis, and a mean posterior movement of the tongue of 5.5 mm compared with 6.5 mm (95% CI 5.3–7.7 mm) in our study, and occlusion in three of 10 patients. In contrast, we have failed to demonstrate obstruction between tongue and posterior pharyngeal wall in a single patient, except during attempted inspiration.

The similarity of our results to those of Morikawa in other respects suggests that anaesthesia, even without paralysis, markedly re-

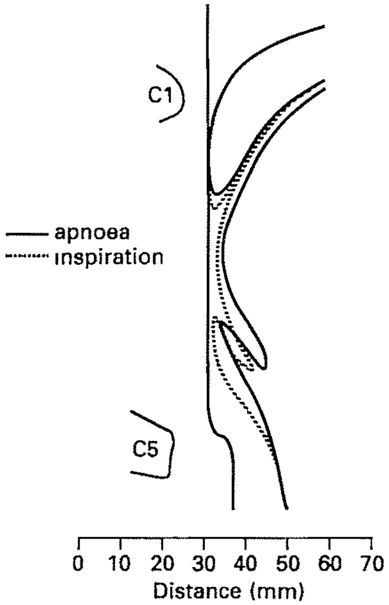

FIG. 4. Changes in pharyngeal outline in attempted inspiration during anaesthesia, but with the head and jaw in neutral position.

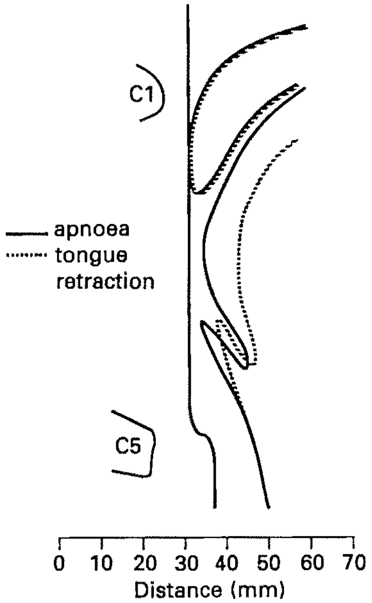

FIG. 5. Changes in pharyngeal outline during anaesthesia when firm traction was applied to the tongue. Note that the outline of the soft palate is unchanged.

duces tone in the muscles of both the tongue and soft palate. There is a relative wealth of published data on muscle and neural activity in the tongue; it is known that electrical activity is present in genioglossus in the awake state [11, 12], and there is evidence in the cat for selective depression of the genioglossus electromyogram (relative to the diaphragm and intercostal muscles) under halothane anaesthesia [4], probably because of selective depression of hypoglossal nerve activity [5]. However, the relevance of genioglossus activity *per se* to airway obstruction under anaesthesia seems questionable in the light of our findings. Drummond [13] has failed also to demonstrate any correlation between genioglossus activity and airway patency in anaesthetized human subjects, and draws attention to the potential influence of complex interactions of various muscle groups on airway obstruction. So far as the soft palate is concerned (which on the basis of our findings may have greater relevance to airway obstruction under anaesthesia), there is no published work of which we are aware investigating the effects of anaesthetics on palatal neural or muscular activity.

The impression that the tongue is principally responsible for airway obstruction in the anaesthetized patient has probably been reinforced by the common observation that insertion of an artificial oropharyngeal airway usually relieves the obstruction. In fact this manoeuvre would be effective, even if the obstruction were solely at the nasopharynx, by providing an alternative route for airflow via the mouth rather than the nose. It is also possible that an occluded nasopharynx might contribute to airway obstruction even if the mouth was open, if the free edge of the tongue were to make a seal against the alveolar arch of the maxilla; this form of obstruction by the tongue would not be amenable to detection by lateral radiography.

There are several mechanisms by which the soft palate might occlude the nasopharynx after induction of anaesthesia. Tonic activity in palatoglossus and palatopharyngeus, perhaps in conjunction with tensor veli palatini, may be responsible for holding the palate away from the posterior pharyngeal wall in the awake state, and it is likely that anaesthesia abolishes or reduces activity in these muscles. Alternatively, anaesthesia (without paralysis) might activate levator palati as it does for the abdominal muscles [14]. However, the similarity of our results to those of Morikawa, Safar and DeCarlo [3] militates against this. A third possibility is derived from the presumed diminished activity of genioglossus. Posterior movement of the tongue, which we have demonstrated in the present study, could result in secondary posterior displacement of the soft palate, either by direct pressure or as a result of posterior movement of the glossal origins of palatoglossus. Our observations on the effect of tongue traction (fig. 5) would seem to exclude this factor as a major influence. Subsidiary factors which we have not investigated include gravity, as suggested by Tomlin and Roberts [10], and surface adhesion between soft palate and posterior pharyngeal wall.

The study by Sivarajan and Fink [15], reporting anterior movement of laryngeal structures with anaesthesia, does not accord with our observations. However, their measurements from the third cervical vertebra would be at a variable angle to the cephalo–caudal axis and would therefore be influenced variably by caudad, in addition to anteroposterior, shifts of the epiglottis and hyoid.

In the light of our findings, it is not clear why artificial oral airways fail so often to provide a clear airway unless neck extension or jaw protrusion (or both) are used. It may be that, on the occasions when such devices fail, their tip is not within a clear airspace (as we have observed radiologically on one occasion); alternatively, these cases may represent obstruction by the epiglottis [8]. It is also possible that the configuration of the tongue may be altered by the airway in a manner that predisposes to airway obstruction. In any event, it seems likely that the nature of the obstruction varies between patients. Further studies will be required to determine why neck extension, jaw protrusion, or both, are often necessary when an artificial oral airway is in place.

The use of conventional radiography as a tool for exploring the upper airway clearly has the limitation of applying a two-dimensional imaging technique to a three-dimensional structure. Hence lateral channelling of airflow might theoretically occur in the presence of apparent midline occlusion. However, it is difficult to see how occlusion could exist in the presence of apparent patency on the radiograph. We therefore conclude that, in our series, the tongue was not responsible for airway obstruction, and that the soft palate would appear to have been the prime site, with possibly some contribution from the epiglottis. Attempted inspiration in the face of upstream obstruction causes major secondary pharyngeal collapse (fig. 4), as in obstructive sleep apnoea [16, 17].

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NITROUS OXIDE AND FORMIMINOGLUTAMIC ACID: EXCRETION IN SURGICAL PATIENTS AND ANAESTHETISTS

P. ARMSTRONG, P. W. H. RAE, W. M. GRAY AND A. A. SPENCE

SUMMARY

We have investigated the possible toxicity of nitrous oxide on vitamin B_{12} and its sequelae upon folic acid metabolism using the urine formiminoglutamic acid excretion test, an index of the functional state of folate metabolism. Ten control subjects not exposed to nitrous oxide and five patients receiving limb surgery under local anaesthesia excreted normal amounts of formiminoglutamic acid in urine for 6 days. Fifty patients received nitrous oxide anaesthesia for similar surgery and, of these, 22 had a dose-dependent increase in excretion on the first 2 days after operation. There were large individual variations. Exposure to 70% nitrous oxide appeared to cause abnormal metabolism of folate when exposure was greater than 90 min. Ten anaesthetists demonstrated normal excretion of formiminoglutamic acid; their exposure to nitrous oxide was typical of that in other studies of theatre environmental pollution.

KEY WORDS

Anaesthetic gases: nitrous oxide. Enzymes. methionine synthase. Vitamins: vitamin B_{12}, folic acid Operating rooms: pollution. Occupational safety: theatre health hazards.

Humans are exposed to nitrous oxide either acutely in high concentrations during general anaesthesia, or chronically in trace amounts from occupational exposure. It is postulated that, in some patients after surgery, this acute exposure may inhibit DNA synthesis, with consequent bone marrow depression and impaired resistance to infection. Investigations into this possibility have assessed the ability of exposed patients to synthesize new DNA, using the deoxyuridine suppression test [1] and direct assaying of liver methionine synthase activity [2]. Both methods are invasive, requiring bone marrow aspiration or liver biopsy.

Nitrous oxide inhibits methionine synthase [2, 3] by oxidation of the cobalt atom [4] in its cofactor, vitamin B_{12}. Methionine synthase plays a pivotal role in folate metabolism; it is the only method of regenerating tetrahydrofolate (THF) from methyl-THF [5]. Its inhibition causes an alteration in the composition of the folate pool, with both an increase in methyl-THF and a decrease in THF [6, 7]. If severe, this alteration interferes with DNA synthesis [8] because of decreased synthesis of deoxythymidine, one of the base precursors of DNA.

The functional state of the folate metabolic pathway may be assessed by examination of the urinary excretion of formiminoglutamic acid (FIGlu) [9–12]. Histidine is catabolized to FIGlu, which requires THF for further catabolism to glutamic acid. THF accepts the formimino group to form 5N-formimino-THF. When a deficiency of THF occurs, FIGlu cannot be metabolized fully and it accumulates in the plasma. Being water soluble, it is excreted in the urine. Small amounts are excreted normally and an increase in excretion occurs with THF deficiency. To expose minor abnormalities and to obviate the effects of diet [13], the histidine catabolic pathway may be stressed by ingestion of oral histidine [12]. This

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test gives a quantitative assessment of the functional state of folate metabolism [14–16].

We have used this relatively non-invasive FIGlu test to investigate the possibility that exposure to nitrous oxide, either during general anaesthesia or occupationally by anaesthetists, may cause abnormality in folate metabolism.

SUBJECTS AND METHODS

Approval for the study was granted by the local Ethics Committee and full informed consent obtained from all subjects. Urinary excretion of FIGlu was measured in all subjects in four groups. The control group consisted of 10 healthy subjects, not exposed to nitrous oxide. The surgical groups consisted of 55 patients undergoing limb surgery of at least 60 min duration: 50 (nitrous oxide group) received general anaesthesia including nitrous oxide; five (local anaesthetic group) received local anaesthesia. None had preexisting renal or hepatic disease. The fourth group (anaesthetists) was composed of 10 anaesthetists who had been working full-time for at least 6 months. All subjects had full biochemical and haematological screening, including urea, creatinine, electrolytes, liver function tests, calcium, albumin, haemoglobin, red blood cell indices, white blood count, vitamin B_{12} and plasma and red blood cell folic acid concentrations. None was taking any drug known to interfere with folate metabolism.

Sample collection. The 10 control subjects were examined over 5 consecutive days. The 55 patients undergoing surgery were examined for 6 consecutive days, starting on the day before operation and continuing from the operative day to the 4th day after operation. The anaesthetists were examined daily for 7 consecutive days, starting at the beginning of the week. All anaesthetists carried out their normal daily work load.

Histidine loading. L-Histidine monochloride monohydrate 10 g was dissolved in 50 ml of either water or orange juice. Full dissolution in cold liquid was slow. The solution was drunk immediately, in the morning by the patients and in either the morning or the evening by the control subjects and anaesthetists.

Urine collection. Before ingestion of histidine, the bladder was emptied and all urine passed during the next 8 h [16] was collected in a plastic container, the bladder being emptied at the earliest convenient time subsequently. Concentrated hydrochloric acid 5 ml was added to each container to prevent decomposition of FIGlu [10]. The volume of each urine specimen was measured.

FIGlu estimation. FIGlu was measured by an established enzymatic method [17]. Standard solutions of urine samples were incubated at room temperature with the enzymes FIGlu transferase and formimino-THF cyclodeaminase (FIGlu enzymes, Sigma Chemical Company) in the presence of THF in the dark. The product of these enzymatic reactions is N^5, N^{10} methenyl-THF, which readily undergoes hydrolysis to N^{10} formyl-THF. The addition of 10% perchloric acid at the end of the enzyme incubation converted any hydrolysed product back to N^5, N^{10} methenyl-THF, which has an absorbance peak at 350 nm. Blanks were performed in parallel with all standards and the samples, differing only in that no enzyme was added. The absorbance at 350 nm of the blanks was subtracted from that of the appropriate standard or sample, and the concentrations in the samples estimated from a standard curve. The linearity of the assay extended beyond the working range required, and the absorbance of a standard solution of FIGlu agreed well with the calculated target value. The within-assay and between-assay coefficients of variation were 8% and 10%, respectively.

Anaesthetic. Both general and local anaesthetic techniques comprised oral temazepam 20 mg as a premedication 1 h before induction of anaesthesia with approximately 4 mg kg^{-1} of thiopentone; suxamethonium was given to aid tracheal intubation. Maintenance of anaesthesia was with 70% nitrous oxide in oxygen; enflurane was given in addition as required. The duration of inhalation of nitrous oxide was noted. Nitrous oxide was given within 6 h of the histidine load. Papaveretum 10–20 mg was given i.v. and also used i.m. in the same dose for relief of postoperative pain. Local anaesthesia comprised either spinal or extradural injection of 0.5% heavy bupivacaine and 0.5% bupivacaine, respectively.

Exposure to nitrous oxide. Each anaesthetist's daily exposure to nitrous oxide was measured using passive diffusive samplers attached to the

TABLE I. *Subject data for control and patient groups (mean (SD)). *Significantly different from the other groups (P < 0.001 Student's unpaired* t *test)*

Group	Age (yr)	Weight (kg)	Sex (M·F)
Control (n = 10)	30.1 (7.5)*	71.5 (9.7)	7:3
Nitrous oxide (n = 50)	51.7 (11.8)	69.0 (12.7)	24:26
Local anaesthesia (n = 5)	56.2 (5.1)	73.6 (9.7)	2:3

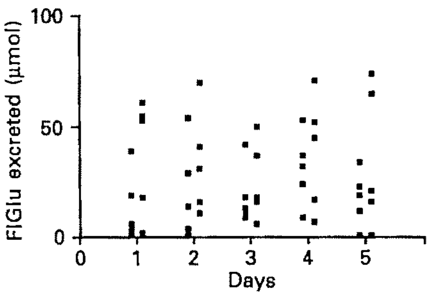

FIG. 1 Daily excretion of FIGlu in 10 control subjects not exposed to nitrous oxide.

theatre tunic near the breathing zone. These provided a time-weighted average exposure over the duration of the operating session [18].

Statistics. Patient and control data were analysed using Student's unpaired t test, as was FIGlu excretion between groups. FIGlu excretion within groups was analysed with ANOVA. Comparison of the mean total daily excretion of FIGlu by each anaesthetist for each of the 7 days and comparison of each anaesthetist's mean total excretion with that of the others was made with ANOVA.

RESULTS

Control subjects

The age of the control group was significantly less than that of the two patient groups (Student's unpaired t test, $P < 0.001$) (table I); however, the age dependence of excretion of FIGlu is small [19], therefore this difference is unlikely to have invalidated comparisons between groups.

All 10 control subjects not exposed to nitrous oxide had normal biochemical and haematological data. All excreted some FIGlu each day (fig. 1), with an overall mean excretion of 27 (SD 22.0) μmol. The range of excretion was wide: 0.3–74 μmol. The mean total excretion of FIGlu for all the 10 controls was similar on each of the 5 days (ANOVA); no cumulative effects occurred. The total mean excretion of each individual control was similar (ANOVA).

Surgical groups

The operations performed on the groups of patients receiving local and general anaesthesia were similar. The local anaesthetic group comprised three total hip and two knee replacements; the nitrous oxide group comprised 17 total hip, 11 elbow and 15 knee replacements, five ankle and foot operations and two removal of infected plates. The duration of surgery for the two groups was similar: mean 111.4 (SD 33.1) min in the local anaesthetic group and 132.3 (56.5) min in the general anaesthetic group.

Local anaesthesia group. All patients receiving local anaesthesia had normal biochemical and haematological data. These subjects excreted FIGlu (fig. 2). on each of the 6 days tested, in amounts within the range previously observed in control subjects. There was no statistical increase in excretion on any of the study days (ANOVA).

Nitrous oxide anaesthesia group. In this group, the duration of anaesthesia was 64–312 min. Preoperative screening was normal in all except one individual who had a low concentration of vitamin B_{12} (194 μmol; normal values are > 220 μmol). On the day before operation and the day of operation (days 1 and 2), all patients except one different individual on each day excreted FIGlu in amounts within the control range (fig. 3) (mean excretion on these days 24.8 (SD 22.3) μmol and 28.9 (23.6) μmol, respectively). However, an increase in excretion of FIGlu occurred on the first day after operation (day 3), when 22 patients excreted concentrations greater than those of the control group (> 80 μmol) (t test: $P < 0.0001$). There was a wide spread of values for FIGlu excreted, with a mean of 78.21 (67.38) μmol. A similar increase in excretion occurred on the next day (day 4), 12 of the 22 individuals excreting more than 80 μmol (t test: $P < 0.0001$ compared with controls). Mean excretion was 61.52 (50.98) μmol.

The increased excretion of FIGlu was dependent partially upon duration of exposure to nitrous oxide; those with increased excretions were exposed to the gas longer (mean 158.6

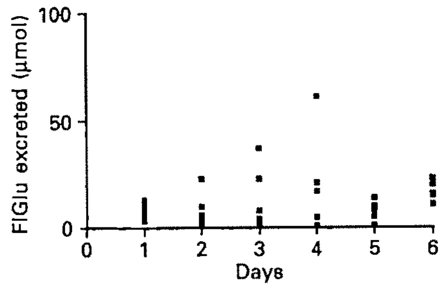

FIG. 2. Daily excretion of FIGlu in five surgical patients receiving a local anaesthetic.

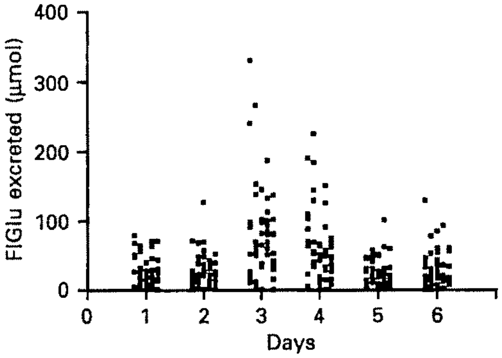

FIG. 3. Daily excretion of FIGlu in 50 surgical patients receiving nitrous oxide anaesthesia.

(64.4) min) than those with normal excretions (mean 113.3 (44.7) min) (Student's unpaired t test: $P < 0.008$). Subjects exposed to nitrous oxide for less than 90 min had normal excretions and all those exposed for more than 211 min had increased excretions.

Excretion of FIGlu returned to control values on the next two days (days 5 and 6), with three and one (different) subjects excreting greater than normal amounts (means 25.49 (21.11) µmol and 29.80 (18.92) µmol, respectively). The patient with a low concentration of vitamin B_{12} had normal FIGlu excretions throughout. The 22 subjects with excretion of FIGlu greater than 80 µmol on day 3 had plasma and red blood cell folate concentrations similar to those with lesser excretions.

Anaesthetists

The mean exposure of each anaesthetist to nitrous oxide was 53.4–159.2 p.p.m. (table II). The mean daily excretion of FIGlu of all the anaesthetists for each of the 7 days (fig. 4) was similar to that of the control subjects (Student's unpaired t test). There was no significant difference in excretion between individuals or between mean total excretions on different days (ANOVA).

TABLE II. *Time-weighted exposure to nitrous oxide for each anaesthetist (mean* (SD) *[range])*

Anaesthetist	Exposure (p.p.m.)
1	135.6 (112.3) [47–325]
2	115.2 (85.7) [22–229]
3	119.8 (134.0) [32–356]
4	60.8 (66.5) [0–139]
5	94.8 (77.4) [0–193]
6	85.2 (86.1) [14–226]
7	159.2 (184.3) [0–413]
8	53.4 (45.5) [0–107]
9	109.8 (166.7) [12–407]
10	58.2 (47.4) [0–114]

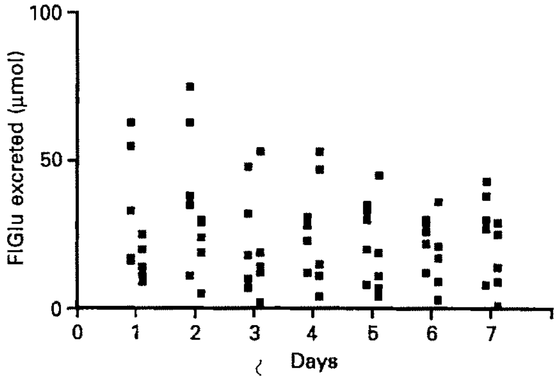

FIG. 4. Daily excretion of FIGlu in 10 anaesthetists occupationally exposed to nitrous oxide.

DISCUSSION

This study has demonstrated that exposure of patients to high concentrations of nitrous oxide during anaesthesia for limb surgery resulted in an increase in excretion of FIGlu on the first two days after operation in some individuals whilst anaesthetists, exposed to trace amounts, had no increase in excretion. Increased excretion was related to the duration of exposure to nitrous oxide and thus appeared to be dose-dependent.

Various workers are exposed chronically to nitrous oxide, including theatre personnel. Pollution of the operating room has caused much health concern [20], although there is little firm epidemiological evidence supporting this [21]. The effect of nitrous oxide is thought to be both time- and concentration-dependent. Rats exposed to the gas continuously throughout pregnancy had increased fetal teratogenicity and resorption at a concentration of 1000 p.p.m., but not at 500 p.p.m. [22]. Intermittent exposures for 6 h per day, 5 days per week increased the threshold to between 1000 and 5000 p.p.m. [23]. Liver methionine synthase activity in rats was found to be unaffected by continuous exposure to concentrations of nitrous oxide less than 450 p.p.m., with an ED_{50} of 5400 p.p.m. [24]. However, extrapolation of these animal studies to man is difficult. Human methionine synthase appears more resistant to nitrous oxide, with an inhibitory $T_{\frac{1}{2}}$ of 46 min, compared with 5.4 min for rats [2]. Moreover, the clinical effects of inhibition of methionine synthase differ between animals and humans [25]. Assessment of the possible dangers of nitrous oxide pollution has relied, therefore, on epidemiological studies of theatre workers, for whom liver biopsy for estimation of methionine synthase activity, and bone marrow sampling for marrow depression testing have obvious drawbacks. Three of 20 dentists exposed to nitrous oxide showed abnormal tests, although their exposure doses were greater than those found normally in theatre [26]. Other work investigating operating theatre workers by examination of peripheral blood films [27] and methionine concentrations [28] obtained negative findings.

Previous studies in patients undergoing nitrous oxide anaesthesia also have involved invasive measurement of methionine synthase activity [2, 29, 30] and investigations of the megaloblastic state of the bone marrow using the deoxyuridine suppression test or by direct morphological studies [31–36]. Therefore there are few studies on the time-course of the effects of nitrous oxide.

Measurement of urinary excretion of FIGlu is a relatively non-invasive procedure, the only unpleasant aspect being the swallowing of the histidine solution. As this technique determines abnormalities in the folate metabolic pathway, it examines different aspects of nitrous oxide toxicity than those based on other methods. It is possible that partial inhibition of methionine synthase assessed in liver biopsies has no clinical significance, whilst abnormalities in bone marrow may indicate that gross biochemical changes have already occurred. Minor changes suggestive of early abnormality may not be revealed using this assay. As the folate pathway links these two biochemical events, investigation here may demonstrate a sensitivity to nitrous oxide toxicity superior to that of examination of the bone marrow, whilst being more clinically relevant than methionine synthase activity. Doses of histidine 10–20 g allow the diagnosis of folic acid deficiency to be made when there is minimal or no megaloblastosis in the marrow [9, 37].

Many regimens for histidine loading have been assessed, with doses of 1–45 g and with urine collections over different time intervals [16]. It has been found that, with the ingestion of 15 g or more, there is a high incidence of nausea and vomiting; with our 10-g loading dose, nine potential subjects were excluded from the study because of nausea. However, histidine 10 g is at least five times the normal dietary intake of histidine [13]. Following a histidine load, most FIGlu is excreted in the urine within 8 h [16].

The FIGlu test has been used in both rats and humans to assess the toxic effects of nitrous oxide. Rats exposed to 50% for 24 h had an increase in urinary excretion of FIGlu [38]. Two of six humans anaesthetized with nitrous oxide at hyperbaric pressures (total dose equivalent to 3.1–7.0 h of 70% nitrous oxide) had increased excretion of FIGlu [39]. We have demonstrated a similar response. Exposure to nitrous oxide for clinical anaesthesia caused an increase in urinary excretion of FIGlu in approximately 50% of subjects. No increase occurred on the day of operation, probably because exposure to nitrous oxide usually occurred long after the histidine load was given and most of the histidine would have been metabolized before the exposure. This is not a surgical effect, as no increase occurred in the local anaesthetic group and it is unlikely to have been caused by a drug other than nitrous oxide, as there has been no report of abnormal folate metabolism with other anaesthetics.

It is not clear why only some individuals are affected by nitrous oxide. Recent evidence implicates the hydroxyl radical scavenger dimethylthiourea as responsible for inactivation of methionine synthase; a hydroxyl radical scavenger protects the enzyme from inactivation by nitrous oxide [40]. It appears that nitrous oxide may react with the cobalt atom in vitamin B_{12} as follows;

$$Co(I) + N_2O \rightarrow Co(II) + N_2 + OH^{\cdot}$$

The hydroxyl radical ($OH^{\cdot}$) may then attack amino acids around the active site of methionine synthase, thereby inactivating it irreversibly [41]. Hydroxyl radicals are highly reactive and readily attack amino acids, especially those that contain sulphur [42]. The cytoplasmic concentrations of intrinsic hydroxyl radical scavengers differ between human individuals, and this may be responsible for different degrees of human susceptibility to nitrous oxide.

The return of FIGlu excretion to normal 72 h after exposure to nitrous oxide is consistent with the irreversibility of the inactivation of methionine synthase, with a requirement for synthesis of new enzyme [43, 44].

One patient had abnormally small concentrations of vitamin B_{12} before exposure to nitrous oxide, although he had no increase in excretion of FIGlu. Nitrous oxide toxicity is increased in animals made deficient in vitamin B_{12} [45]. The reason for the lack of effect in this patient is unknown.

This work demonstrates that exposure to increased concentrations of nitrous oxide for at least 90 min caused an abnormality in the folate metabolic pathway. The eventual consequence of this would be a decrease in DNA synthesis. In humans, exposure to 50% nitrous oxide for at least 6 h is needed for this to be significant; in our study, patients received 70% for up to 320 min and some demonstrated abnormalities in their folate metabolism. The clinical relevance of this result is unclear at present.

In contrast to individuals exposed acutely to increased concentrations of nitrous oxide, in anaesthetists who were exposed chronically to trace concentrations of nitrous oxide, the daily urine excretion of FIGlu was similar to that of the control group; this suggests that theatre pollution by nitrous oxide has no adverse effects on folate metabolism of exposed workers, which is in agreement with two other studies [9, 28].

The target maximum exposure to nitrous oxide set by the United States National Institute for Occupational Safety and Health (NIOSH) is 25 p.p.m. [46], a value which was almost always exceeded in this study. Sharer and others [24] have recommended a safe limit of 200 p.p.m. and it would appear from our study also that the NIOSH limit may be unnecessarily low.

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HUMAN LEARNING DURING GENERAL ANAESTHESIA AND SURGERY†

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SUMMARY

To determine if learning occurs during general anaesthesia, 72 women undergoing surgery were given postoperative implicit memory tests in which performance could be influenced by auditory information presented during general anaesthesia. Two methods of anaesthesia were used: nitrous oxide and opioids (n = 24) or nitrous oxide and isoflurane (1, 1.3 and 1.5 MAC for n = 12, 24 and 12, respectively). Three tests showed some retention, apparently unconscious, of information presented during anaesthesia: in Behavioural Suggestions tests, patients who were instructed during anaesthesia to touch a particular body part (ear or nose) during later questioning touched the "correct" (suggested) body part longer than the "incorrect" (not suggested) body part during a postoperative interview on the day of surgery (means 2.5 vs 0.2 s); in Word Completion tests, patients shown a page containing the first three letters of words and asked to give words beginning with those letters gave more words from a list that had been played during anaesthesia than from a list not played (means 0.48 vs 0.27 words); in Nonsense Word tests, patients who were played different nonsense words between two and 16 times during anaesthesia preferred and guessed more accurately those that had been played most often (16 times) relative to those played less often in subsequent preference and recognition tests (means 56% vs 46% for preference and 62% vs 48% for recognition), while showing no such patterns in additional control tests. Learning did not vary with the method of anaesthesia, as might have been expected if learning was a monotonic function of brain depression. Some information processing functions of the brain evidently continue to function during adequate general anaesthesia.

KEY WORDS

Anaesthesia general, learning, memory. Complications awareness, memory

Although there are anecdotal reports of conscious awareness and recall of operating room conversations during general anaesthesia [1, 2], experiments assessing recall of auditory stimuli presented during anaesthesia have produced no evidence of learning [3,4]. Techniques for assessing learning without conscious awareness have become available recently [5–8] and have proven useful in revealing residual learning abilities in patients with organic amnesias. The small number of studies on learning during anaesthesia using these and related techniques have produced conflicting results [9–13], but the positive findings have been criticized on methodological and statistical grounds [14–17]. The occurrence of learning and unconscious awareness during anaesthesia has practical in addition to theoretical significance: it has been claimed that presentation of appropriate therapeutic suggestions during anaesthesia may improve postoperative recovery, while unfavourable comments may have potentially adverse postoperative effects [18–21].

In this study, we have looked for evidence of capacity for learning during anaesthesia and also if this capacity (if present) varied with the end-expired concentrations of anaesthetics. The assessments included several recently developed "implicit" memory tests which do not assess

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memory explicitly but in which performance may be influenced by previously presented information. In the *Word Completion* and *Constrained Associations* tasks, patients gave words starting with specified letters or belonging to specified categories, respectively. A list of words presented during anaesthesia provided appropriate answers and the assessment indicated how much this presentation ("priming") increased the likelihood of giving those answers. In the *Nonsense Words* task, nonsense words were repeated with varying frequencies. In addition to guessing which nonsense words had been presented, patients decided which sounded more pleasant. Such preference ratings are thought to be affected by frequency of repetition, even when subjects cannot recognize which stimuli have been presented previously [8].

PATIENTS AND METHODS

We used two studies consecutively which differed in anaesthesia methods and assessments of learning.

Study 1

Patients were allocated blindly and randomly to one of two anaesthesia methods. Sixty-seven per cent of the patients assigned to each anaesthesia method were presented with stimuli during anaesthesia for six subsequent assessments of learning. The remaining patients were treated similarly except that, for purposes of comparison, they were presented with stimuli for two of the assessments (Word Completion and Constrained Associations) before rather than during anaesthesia.

Patients were interviewed the day before surgery, and were excluded from the study if the two anaesthesia methods were inappropriate or if they presented with conditions that might interfere with presentation of stimuli or test procedures or otherwise reduce the likelihood of detecting learning, for example hearing disorders or mental impairment. Informed consent was obtained (as approved by the Institutional Review Board of the University of Iowa). Forty-eight women were studied (table I).

Patients who needed preanaesthetic medications were given morphine (mean) 0.13 mg kg^{-1} i.m., 1 h before surgery (33 % of patients) or glycopyrrolate 0.003 mg kg^{-1} i.m., 1 h before surgery (10 % of patients), or both drugs. Anaesthesia was induced with thiopentone 3.0 mg kg^{-1}. For maintenance of anaesthesia, 50 % of patients received isoflurane and 70 % nitrous oxide in oxygen to produce end-tidal concentrations of 1.3 MAC for the two drugs (0.7 % isoflurane). The remaining patients received 70 % nitrous oxide in oxygen with opioids.

Concentrations of the anaesthetic vapours and gases were maintained for at least 15 min to ensure stable end-tidal concentrations. Inspired and expired concentrations or partial pressures of isoflurane, nitrous oxide and physiological gases were measured continuously by a mass spectrometer.

In the group receiving nitrous oxide with opioids, 50 % of the patients received bolus doses and the other 50 % an infusion of opioids. For the regimen with bolus doses, fentanyl 7.5 $\mu g\ kg^{-1}$ (or its equivalent of other opioids) was given before thiopentone. Additional doses of 2.5 $\mu g\ kg^{-1}$ were administered when the systolic arterial pressure or the heart rate increased more than 15 % above the preanaesthetic values or the patient moved. For the regimen with opioid infusion, alfentanil in a dose of 50 $\mu g\ kg^{-1}$ (or its equivalent of other opioids) was administered followed by an infusion at the rate of 1–1.5 $\mu g\ kg^{-1}\ min^{-1}$. The rate of infusion was varied according to the patients' response. We assumed sufentanil 1 μg, fentanyl 5 μg and alfentanil 25 μg to be equivalent doses [22].

Presentation of stimuli during surgery

Tape recordings of stimuli for the six assessments were played to patients via headphones starting 5 min after surgical incision and continuing for 22 min. The stimuli, in the order presented, were as follows:

Word Completion. Two lists of 12 different words were constructed. None of the words on the two lists had the same initial three letters. For each word on the lists, there were at least 10 common words beginning with the same three letters. The two lists were equated in a pilot study using students attending an introductory psychology course [23]. One list was played to 50 % of the patients, the other list was played to the other 50 % at the rate of one word every 5 s.

Constrained Associations. Categories such as "male clothing" and instances of each category such as "vest" and "coat" were chosen using normative data on the frequency with which different instances are given as examples of

TABLE I. *Patient, anaesthetic and surgical details (mean (SEM) or percent of group. No significant differences among the three groups were found by chi-square test (for the frequency distributions) or one-way analysis of variance (for the remaining characteristics). *All recordings were played during operation for Study 1, group A and Study 2. For Study 1, group B the recordings for Word Completion and Constrained Associations were played before operation and the remaining recordings were played during operation. †Sum of preoperative ratings of severity of disease of seven organ systems (respiratory, cardiovascular, nervous, renal, digestive, endocrine/metabolic and muscle/skin/bone). The physiological and functional integrities of each system were classified into three grades of impairment (1 = none, 2 = some, 3 = severe) [30]. The range of possible sums is 7 to 21*

	Study 1		
	Group A* (*n* = 32)	Group B* (*n* = 16)	Study 2 (*n* = 24)
Age (yr)	34 (1)	38 (2)	35 (2)
Education (yr)	13 (0.4)	14 (0.7)	13 (0 6)
Weight (kg)	78 (4)	75 (7)	84 (7)
Total dose of thiopentone (mg kg^{-1})	2.9 (0.3)	3.3 (0.4)	3.4 (0.3)
Duration of surgery (min)	144 (15)	97 (9)	122 (11)
Duration of anaesthesia (min)	173 (16)	123 (9)	151 (10)
Postoperative stay (days)	4.9 (0 4)	4.3 (0.6)	4.5 (0.4)
Health index score†	8.0 (0.2)	8.4 (0.4)	8.5 (0.3)
Frequency distributions (%)			
Race			
White	100	94	100
Black	0	6	0
ASA status			
I	50	50	54
II	44	44	42
III	6	6	4
Types of surgery	28	38	33
Operations on the Fallopian tubes for infertility			
Vertical banding gastroplasty for morbid obesity	6	19	21
Total abdominal hysterectomy	16	6	25
Cholecystectomy	9	6	0
Other small groups	41	31	21

specified categories. Two lists of 12 words, each consisting of four instances from three categories, were constructed. Each list was played to 50 % of the patients at the rate of one word every 5 s.

Nonsense Words. Two lists of 16 distinct nonsense words repeated with varying frequencies (two, four, eight or 16 times) were constructed. Each consisted of pronounceable five-letter consonant-vowel-consonant-vowel-consonant nonsense words (e.g. "picul", "goral") recorded at a 3-s rate. The lists were balanced on normatively rated pleasantness and pronounceability [23]. Each list was played to 50 % of the patients.

First Names. Three first names were presented, with suggestions to think and dream about them. The names were selected randomly from six first names of close relatives obtained from each patient during the preoperative interview.

Behavioural Suggestions. Suggestions to touch an ear during the postoperative interview by the research assistant, were played to 50 % of the patients [9]. Suggestions to touch the nose were played to the remainder.

Postoperative assessments

Neither the patients nor the research assistant who conducted the postoperative assessments were told which stimuli had been played during anaesthesia. Tests were performed on the day after surgery; Behavioural Suggestion was assessed also on the day of surgery.

Behavioural Suggestions. Later on the day of surgery, the research assistant conducted a 4-min structured interview with the patient. During the interview, the research assistant surreptitiously recorded touches of the ear and nose. The research assistant repeated the procedure on the day after surgery, then asked the patient to guess if she had received a suggestion to touch the ear or nose. Following this, the research assistant administered the other assessment tests.

Word Completion. The patient was given a page containing the first three letters (e.g. "con", "pen", "man") of the 24 words on the two lists (e.g. "concern", "pension", "manual") and was asked to give the first word beginning with those letters that occurred to her. The number of words given from the list that had been primed (played during (or before) anaesthesia) and the number of words given from the other list were recorded. An explicit recognition test was given subsequently. The patient heard pairs of words, each pair containing one of the words from the two lists, together with a similar "distractor" word that was not included on either list. The patient was asked to identify the words that had been presented previously, guessing if necessary.

Constrained Associations. The patient was given six categories (e.g. "tree", "male clothing") and asked to give eight examples for each. The categories were those from which the words on the two lists had been selected (e.g. "hickory", "spruce", "vest", "coat"). Again, the number of words given from the list that had been played during (or before) anaesthesia and the number of words given from the other list were recorded. Also, an explicit recognition test was given subsequently, similar to the previous task.

First Names. The patient was asked to select, from the six first names she had provided before operation, the three that had been played during anaesthesia.

Nonsense Words. The patient heard pairs consisting of one nonsense word that had been played during anaesthesia and one that had not (e.g. "picul"–"ratal"). She guessed which had been played and, during a separate presentation, decided which sounded more pleasant. The order of administration of the preference and recognition tests was balanced between patients. As an additional control for any inherent differences among particular nonsense words in pleasantness or familiarity, these preference and recognition tests were administered to each patient using the nonsense words from the second list, none of which had been played to her previously.

Study 2

The assessments that showed no evidence of memory for information presented during anaesthesia in Study 1 (Constrained Associations and First Names) were discontinued and the tape recordings of stimuli for the remaining assessments were repeated throughout anaesthesia until the target concentrations of anaesthetics were changed toward the end of surgery. Greater and smaller concentrations of isoflurane than used in Study 1 were administered. The postoperative assessments were the same as in Study 1. Changes from the procedures of Study 1 were as follows:

Twenty-four women were tested. Characteristics of these patients and those included in Study 1 were similar (table I).

Isoflurane and 70% nitrous oxide in oxygen were administered to produce combined end-tidal concentrations for the two anaesthetic drugs of 1.5 MAC (0.8% isoflurane) for 50% of the patients and 1 MAC (0.5% isoflurane) for the remainder. If 1 MAC proved insufficient as shown by an increase in arterial pressure, an increase in heart rate, muscle movements or other signs of light anaesthesia, bolus doses of opioids were administered as needed, as in Study 1.

Statistical analyses

The data were submitted to analyses of variance to determine if there was implicit or explicit memory for information presented during anaesthesia. In Behavioural Suggestions, touches of both the nose and ear were scored for each patient; a between-subjects factor represented if the nose or ear was mentioned in the intraoperative suggestion given to each patient and a within-subjects factor represented the patient's two scores, one for the "correct" (suggested) body part and the other for the "incorrect" (not suggested) body part. A significant main effect of the latter factor (more touching of the suggested body part) would indicate that the intraoperative suggestion affected behaviour and thus provide evidence of learning during anaesthesia. Similarly, in Word Completion and Constrained Associations, the number of words given from the two lists was counted for each patient; a between-subjects factor represented which of the lists was played to each patient and a within-subjects factor represented the patient's two scores, one for the list played to her and one for the other list. A significant effect of the latter factor (more words given from the list that was played) for the patients to whom the lists were played during operation would provide evidence of priming and, consequently, of learning during anaesthesia. Data from the control patients to whom the lists were played before anaesthesia were analysed separately. Similar analyses were made for the explicit recognition tests of the words played for Word Completion and Constrained Associations (and for the First Names test, but in this case there was only one score per patient).

The data from both Studies 1 and 2 were pooled for these analyses, which included a factor representing the anaesthesia methods and procedural differences between Studies 1 and 2 (nitrous oxide and opioid anaesthesia and 1, 1.3 and 1.5 MAC nitrous oxide and isoflurane anaesthesia). Additional analyses were made comparing the two methods of opioid administration (infusion *vs* bolus) for nitrous oxide and opioid anaesthesia. As methods of opioid administration, anaesthesia methods and procedural differences between Studies 1 and 2 did not produce any significant effects on performance in any test, the analyses of methods of opioid administration are omitted from this report and analyses of the pooled data from Studies 1 and 2, excluding the anaesthesia method factor, are reported.

The analyses of the preference and recognition tests for Nonsense Words in Study 1 included an additional within-subjects factor representing the frequency of repetition of the nonsense words on the recordings played during operation (two, four, eight or 16 times). Each patient contributed scores from both the experimental test (on the recording played to her during operation) and the control test (on the recording played to other patients). A significant interaction of frequency of repetition with test (experimental *vs* control) would provide evidence of learning during anaesthesia.

The Nonsense Words results for the patients in Study 2, to whom the tape recording of nonsense words was repeated a variable number of times (proportional to the duration of each patient's surgery), were not amenable to statistical analysis because frequency of repetition was confounded with variability among patients—that is, a patient undergoing a short operation received from two to 16 repetitions of different nonsense words, whereas a patient undergoing surgery long enough to repeat the entire tape six times received from 12 to 96 repetitions of different nonsense words. Despite this unfortunate limitation, the number of repetitions of nonsense words for each patient could still be estimated and checked for consistency with the results of Study 1.

For Behavioural Suggestions, a chi-square test was used to assess patients' retrospective guesses about which body part had been mentioned in the intraoperative suggestion. For duration of touches, Wilcoxon's signed rank test was used, to check that significant effects in the analysis of variance were not caused solely by a few very long durations.

RESULTS

The patients in Studies 1 and 2 did not differ significantly in the potentially confounding characteristics shown in table I, although the patients in Study 1 who were played the lists for Word Completion and Constrained Associations before operation tended to have surgery of shorter duration. None of the patients showed obvious signs of wakefulness during anaesthesia such as opening the eyes or moving the limbs in a purposeful manner. After operation, none reported any recall of words, nonsense words, conversations or sounds during anaesthesia. The explicit recognition tests for the First Names task and for the words in the Word Completion and Constrained Associations tasks showed no evidence of learning during anaesthesia, nor did patients' retrospective guesses about which body part they had been asked to touch in Behavioural Suggestions.

The implicit tests in Word Completion, Behavioural Suggestions and Nonsense Words showed evidence of learning during anaesthesia.

Priming occurred in Word Completion (fig. 1): the average patient gave more words from the list that had been played to her during anaesthesia (mean 0.48 words) than from the list not played (0.27 words) ($F_{1,54} = 4.3$; $P < 0.05$). The effect was very small: 34% of the patients gave more words from the list played during anaesthesia than from the other list, while 18% showed the opposite pattern and 48% showed no difference (generally giving no words from either list). Priming did not vary depending on anaesthesia method or if the list was repeated during an-

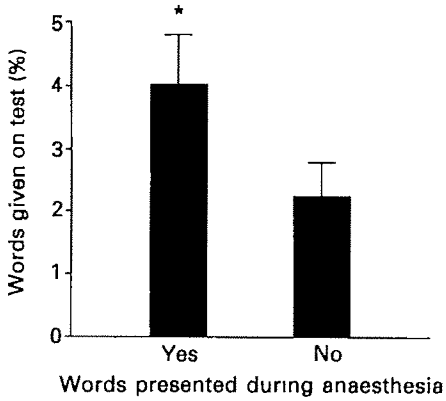

FIG. 1. Performance in the Word Completion task. The values are the percentages of words given on the test by the average patient from the list that had been played to her during anaesthesia ("Yes") and from the list not played to her ("No"). The priming effect is the difference between these values. The patients in Study 1 to whom the Word Completion lists were played before rather than during anaesthesia are not included. Error bars indicate 1 SE. $*P < 0.05$ by analysis of variance.

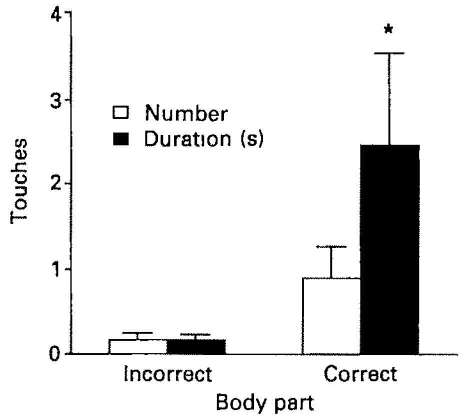

FIG. 2. Performance in the Behavioural Suggestions task during 4 min of postoperative questioning on the day of surgery. The values are the number and duration of touches by the average patient of the body part that had been specified in the suggestion played to her during anaesthesia ("Correct") and of the other body part ("Incorrect"). Error bars indicate 1 SE. $*P < 0.05$ by analysis of variance.

aesthesia or played only once. In the former case, the average patient gave 0.17 more words from the list played during anaesthesia than from the list not played; in the latter case, the corresponding figure was 0.25 words.

In contrast, priming in the Constrained Associations task (Study 1) showed no evidence of memory for information presented during anaesthesia. Patients in Study 1 who were played the Constrained Associations and Word Completion tapes before rather than during surgery showed evidence of recognition, but not priming, the next day.

In the Behavioural Suggestions task, during questioning on the day of surgery, patients touched the "correct" (suggested) body part longer than the "incorrect" (not suggested) body part ($F_{1,41} = 4.5$; $P < 0.05$) (fig. 2). The mean durations were 2.5 s and 0.2 s, respectively. This effect provided evidence of learning during anaesthesia, but was attributable to only a fraction of the patients: in contrast to the 23% of patients who touched the "correct" body part longer than the "incorrect" body part, 7% touched the "incorrect" body part longer than the "correct" body part, while the remaining 70% did not touch either body part. A few patients showed very long durations of touching the "correct" body part, but the effect was not caused solely by these long durations skewing the data; it was also significant by Wilcoxon's signed rank test ($P < 0.05$). The number of touches showed a marginal trend in the same direction—more touches of the "correct" body part than the "incorrect" part ($F_{1,41} = 3.8$; $P = 0.06$; means of 0.9 and 0.2 touches, respectively). The difference in duration of touching the "correct" and "incorrect" body parts did not vary significantly depending on anaesthesia method or if the tape recorded suggestions were repeated during anaesthesia (difference = 0.7 s) or played only once (difference = 2.7 s). The effect of suggestions was not present on the day after surgery.

Both the preference and recognition tests for Nonsense Words showed evidence of learning during anaesthesia in Study 1, in which the tape recording of nonsense words repeated with varying frequencies was played only once (fig. 3). Patients both preferred and guessed more accurately those nonsense words that had been played to them most frequently (16 times) during anaesthesia relative to those played less frequently (two, four or eight times), but showed no such patterns in the additional control tests, indicating that the experimental effects were not attributable to inherent differences among particular nonsense words in pleasantness or familiarity ($F_{3,141} = 3.2$; $P < 0.05$ for the preference test and $F_{3,132} = 3.3$; $P < 0.05$ for the recognition test). For nonsense words presented during anaesthesia, the scores were 56% for preference and 62% for recognition

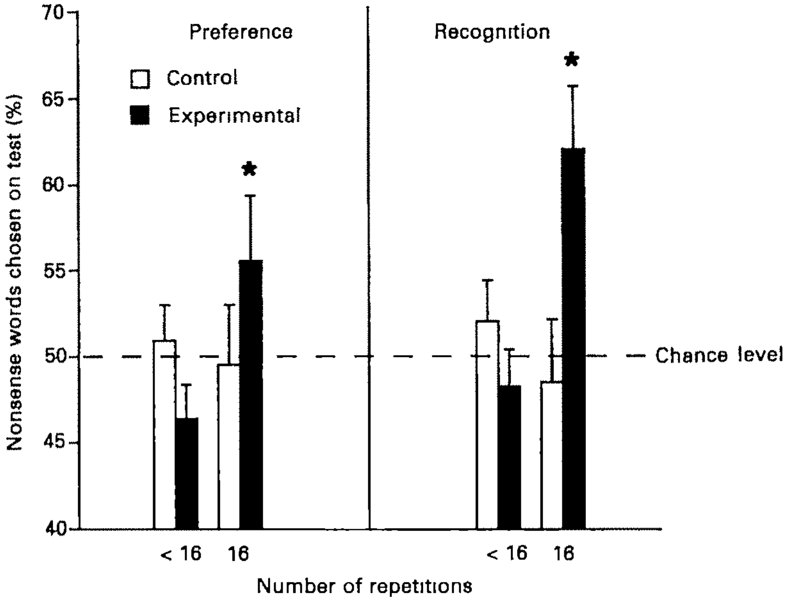

FIG. 3. Performance in the Nonsense Words task. Values are the percentages of nonsense words chosen by the average patient on the preference and recognition tests for nonsense words from the list that had been played to her during anaesthesia ("Experimental") and from the list not played to her ("Control"). The values are for Study 1, in which the tape recording of nonsense words repeated with varying frequencies was played only once, and are shown separately for the nonsense words that were repeated the most times ("16") and fewer times ("< 16") during anaesthesia. The dotted line shows the expected values if patients had guessed randomly (50%). Error bars indicate 1 SE. $*P < 0.05$ by analysis of variance.

with 16 repetitions and 46% and 48%, respectively, with fewer repetitions. The corresponding percentages in the additional control tests were 49%, 49%, 51% and 52%, respectively. The effects on preference and recognition did not vary depending on anaesthesia method.

The Nonsense Words results for the patients in Study 2, to whom the tape recording of nonsense words was repeated a variable number of times, were consistent with those of Study 1 for the preference test, but not the recognition test. For nonsense words that were chosen correctly on the preference test, the average estimated number of repetitions during anaesthesia was 37, compared with only 33 for nonsense words that were not chosen correctly. The corresponding figures for the recognition test were 33 and 38, respectively.

DISCUSSION

Recent findings in amnesic patients suggest that there are two types of memory: explicit (or declarative) and implicit (or procedural or non-declarative) [5, 24]. Explicit or declarative memory embraces that which may be declared or brought to mind as a proposition or image. It is measured by recall and recognition tests, which usually involve conscious or intentional recollection. Implicit or non-declarative memory refers to a heterogeneous collection of memory phenomena which do not necessarily require conscious recollection, including retention of motor skills and priming, the facilitation of performance by prior exposure of stimuli, as in the Word Completion task. Amnesic patients have markedly impaired explicit memory but their implicit memory is spared.

The results of the Word Completion, Nonsense Words and Behavioural Suggestions tasks showing implicit memory for information presented during anaesthesia were small in magnitude and attributable to only a fraction of the patients. Nevertheless, they show evidence of a potential for learning during anaesthesia. All the tests were controlled by producing two sets of materials (words, nonsense words or suggestions) and presenting them during operation to different patients, with subsequent testing of patients on both sets of materials under double-blind and randomized conditions. The registration of information under anaesthesia must be feint and its storage so fragile [25] that even with sensitive tests, the evidence is inevitably not robust.

The recognition by the patients in Study 1 of those nonsense words that had been played most frequently (16 times) during anaesthesia might be interpreted as suggesting conscious memory of anaesthetic experience. This seems unlikely because the patients viewed their recognition judgements as pure guesswork, the greater-than-chance judgements might have been mediated by automatically encoded frequency information [26, 27] and the Nonsense Words results of Study 2, although they cannot be interpreted with confidence, suggest that learning may be detected more reliably with the implicit, preference test than with the recognition test.

Priming occurred, providing evidence of learning during anaesthesia, in the Word Completion task but not in the Constrained Associations task. The relation between the test cues and the words played during anaesthesia was more direct in Word Completion (e.g. "bal"—"balance") than Constrained Associations (e.g. "metal"—"chromium"). Perhaps a direct relation is best for detecting learning during anaesthesia. A previous study [10] found no evidence of learning during anaesthesia using another type of priming test which required a higher level cognitive skill (inferring the intended meaning and spelling of a word from associative context).

A separate control group seemed desirable only for the Word Completion and Constrained Associations tasks, in case there was no evidence of priming with intraoperative presentation of materials. Contrary to assessments of the effects of anaesthesia on priming, which have received little attention, the available literature strongly suggests that preanaesthetic presentation of first names and nonsense words would not impair postoperative recall and recognition. In fact, while intraoperative priming occurred in Word Completion, the patients who were played the Word Completion and Constrained Associations tapes before surgery showed explicit memory, but not priming, the next day. Priming decreases and eventually vanishes as the delay between presentation and test increases [6, 7]. Evidently, priming was not as long-lasting with preoperative presentation to patients as it was for healthy volunteers in a previous study of ours, which involved a comparable delay [23]. Patients in the latter study were given a semantic orienting task (rating how much they liked or disliked the words) to focus their attention on the material. The omission of this task in the present study, combined with the stress of impending surgery, may explain the absence of long-lasting priming.

A previous study [9] of Behavioural Suggestions was criticized [17] for lacking a baseline or pretreatment assessment. The same could be said of our study; however, we introduced an additional control not used previously [9, 11]: giving a suggestion to touch the ear to 50% of the patients and a suggestion to touch the nose to the remainder, then measuring both ear-touching and nose-touching in all patients. The patients given a suggestion to touch the ear provided a measure of nose-touching in the absence of a suggestion to touch the nose, and *vice versa*. Previous findings with Behavioural Suggestions [9] have also been criticized [17] because the difference between the experimental and control groups was a result of extreme results in two patients. In our study, also, a few patients showed very long durations of touching the suggested part, but the effect was not caused solely by these long durations skewing the data.

We found that learning did not vary with methods of anaesthesia. This seems to contradict the widespread, plausible belief that "light" relative to "deep" anaesthesia increases the likelihood of retention under anaesthesia, as would be expected if brain mechanisms necessary for learning were depressed progressively with increasing anaesthetic concentrations. However, it has been suggested that unconscious, implicit memory, in contrast to explicit memory, may be influenced less by the methods of anaesthesia and the doses of drugs [21, 28–29]. Our results support this suggestion, but need to be confirmed with a larger number of patients, as an influence of anaesthesia method on learning could have been missed in the present study because of the small sample size, together with the small size of the learning effects themselves.

The results of our research support the view that some information processing functions of the brain that are normally associated with conscious awareness, such as language comprehension and learning, may continue to function during adequate surgical anaesthesia. More work is needed to replicate these results, and to assess their implications.

ACKNOWLEDGEMENT

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EFFECT OF LOW CONCENTRATIONS OF NITROUS OXIDE AND ISOFLURANE ON PEAK VELOCITY OF SACCADIC EYE MOVEMENTS

F. GAO, R. W. MARSHALL AND M. D. VICKERS

SUMMARY

Peak velocity of saccadic eye movements was studied in six healthy volunteers who were each given, on separate days, 5% and 10% MAC of nitrous oxide (5% and 10% end-tidal) or of isoflurane (0.06% and 0.12% end-tidal) or air, each gas for 25 min. Subjective assessment following each treatment was also undertaken. No significant difference was found between air and either 5% or 10% nitrous oxide. However, significant differences occurred at 15 and 25 min after 0.06% isoflurane compared with air ($P < 0.05$*) and highly significant differences were present 5, 15 and 25 min after 0.12% isoflurane when compared with air and nitrous oxide (*$P < 0.01$*). In contrast, there was little difference between the three gases by subjective assessment.*

KEY WORDS

Anaesthetic gases. nitrous oxide. Anaesthetics, volatile isoflurane. Brain · saccadic eye movements.

There is now substantial evidence that the peak velocity of saccadic eye movements is an indicator of the function of a well defined group of neurones in the brainstem reticular formation [1]. Published studies suggest that saccadic eye movements are a sensitive indicator of CNS depression, as their analysis has been used successfully to measure central effects of benzodiazepines [2], opioids [3], alcohol [4], barbiturates and non-barbiturate anticonvulsants [5]. Thus they might form a method of indicating fitness for discharge of patients after day-case anaesthesia. However, there appears to have been only one paper on the effect of inhaled anaesthetics on peak saccadic velocity, and that was inadequate [6].

The present study was designed to determine if subanaesthetic concentrations of nitrous oxide and isoflurane affected peak saccadic velocity, if the effects were the same for both agents and if there was a dose–effect relationship. Nitrous oxide and isoflurane were chosen for initial study because of their low solubility and the possibility of reaching a steady alveolar–arterial difference within a reasonable time.

SUBJECTS AND METHODS

Six healthy volunteers aged 22–32 yr gave written informed consent for this study, which was approved by the Ethics Committee of the Division of Anaesthetics.

Breathing system

Each volunteer wore a Royal Air Force pilot's face-mask with a non-rebreathing valve. A plan of the breathing system for the administration of the inhalation agents is shown in figure 1. Total fresh gas flow was 10 litre min^{-1}. An Ambu valve was inserted into the inspired limb of the breathing system to avoid the expired gas being diluted by excess fresh gas. A 180-cm length of tubing of 2.5 cm diameter was attached to the expiratory valve of the mask, from which samples of expired gases were drawn.

Three different test gases were used: nitrous oxide, isoflurane and air (control). When the test gas was air, the subject breathed air through the mask throughout the session.

Nitrous oxide mixtures were made by blending Entonox (50% nitrous oxide in oxygen) with air. The flowmeters were calibrated for Entonox and for air with a Harvard Dry Gas Meter. The

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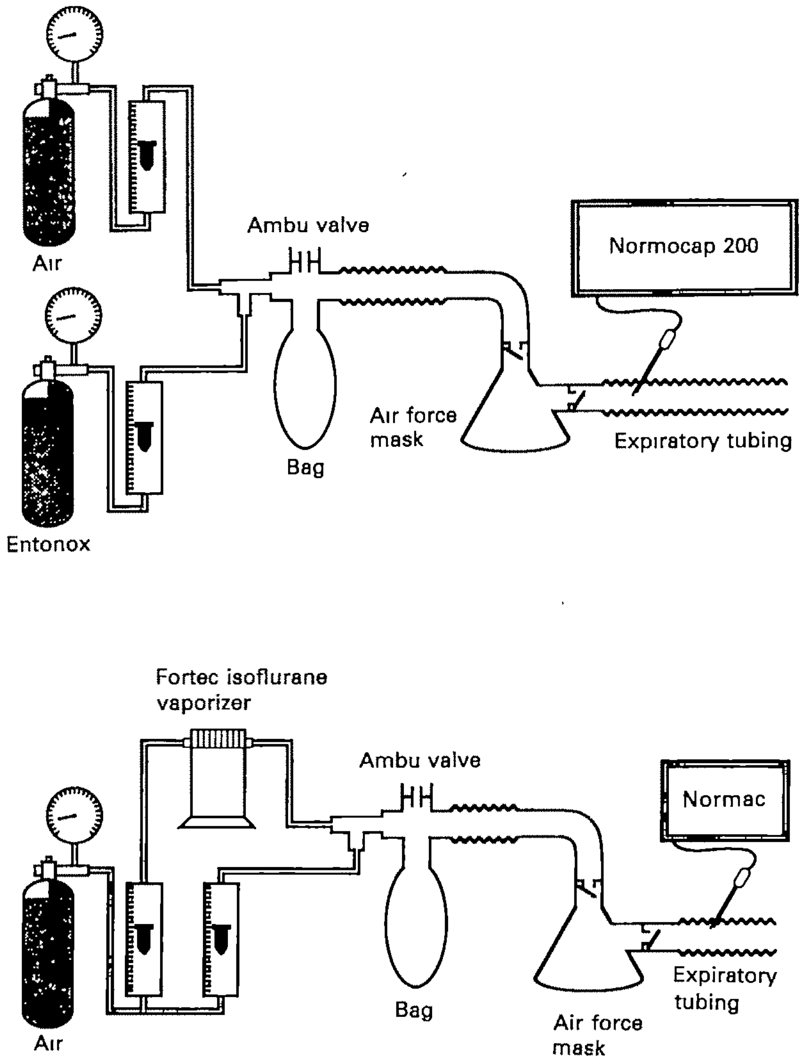

FIG. 1. Diagram of the breathing system for the administration of nitrous oxide and isoflurane.

maximum error was ±5% of the predicted reading. The concentration of end-tidal nitrous oxide was measured breath-by-breath with a Normocap 200 infrared analyser and the flowmeters adjusted to achieve the desired concentrations. The Normocap 200 was calibrated and recalibrated with known 2%, 5%, 10% and 25% mixtures of nitrous oxide delivered from the calibrated flowmeters.

The required isoflurane concentrations were obtained by using a calibrated Fortec isoflurane vaporizer and diluting the output concentrations with air via a second calibrated flowmeter. Again, inspired concentrations were adjusted in order to maintain the required end-tidal concentrations. Isoflurane standards in the range 0.01–1.5 vol% were prepared in gas tight glass jars of known volume using a weighted aliquot of liquid isoflurane and treating the vapour as if it were an ideal gas. These standards were used to calibrate a Datex Normac preset to measure halothane concentrations. The concentrations were displayed on a two-channel chart recorder [7]. Occasional samples of end-tidal gas were checked for isoflurane concentrations by gas chromatography. The results agreed with those obtained from the Normac, which was zeroed before each measurement.

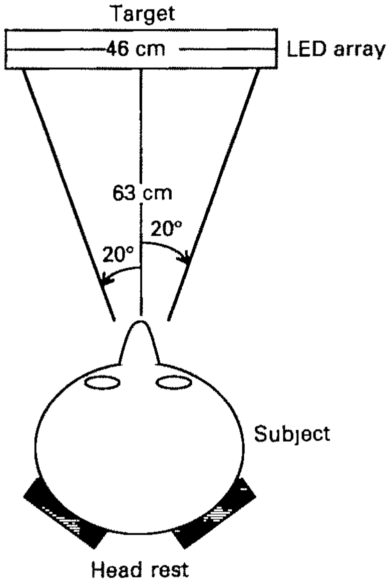

FIG. 2. Saccadic eye movements generated in the laboratory by instructing a subject to follow a luminous target which is made to jump instantaneously from one point to another.

Saccadic eye movement measurements

Saccades were generated by having the subject follow the movements of an illuminated target which was presented on a linear array (46 cm long) of 110 bar-shaped light-emitting diodes. The subject was seated 63 cm from the target array with the head restrained by a head rest which allowed a maximum symmetrical target displacement of 20° either side of the mid-line, or 40° in all (fig. 2).

Saccadic eye movements can be analysed in several ways. To obtain reliable measurements of peak velocity, the subject must be instructed that the objective is not to move the eyes as quickly as possible, but just to follow the movement of the target. When the subject has initiated a saccade, the saccade is not under voluntary control. Each measurement consisted of three sequences, each of 25 target movements. The target movements took place at 1.5-s intervals and each sequence therefore lasted 38 s, with a 20-s rest period between sequences. Measurements taken in each sequence were five displacements each at 40°, 35°, 30°, 25° and 20°. Thus, at each displacement angle, there were 15 analysable saccades. Four extra 40° displacements were presented before each sequence, to allow the subject to settle.

Eye position was monitored from the electro-occulogram (EOG). The eyeball is electrically polarized, positive anteriorly and negative posteriorly; this arises from the activation of the retina by light [8]. Horizontal deflection of the eyeball changes the d.c. potential of the EOG and this change is proportional to the angular displacement of the eyeball. The EOG was measured between two silver–silver chloride electrodes placed on the outer canthi of each eye and an indifferent electrode placed on the forehead. Electrode resistances were always less than 4 kΩ. The EOG was d.c. amplified and low-pass filtered (−3 dB at 50 Hz) before being digitized to 12-bit resolution at a sampling frequency of 250 Hz.

An IBM compatible (Opus PC II) micro-computer controlled the target movements and digitized the waveform using an A–D converter. The computer also stored the EOG data on disk to await analysis.

Saccade analysis was carried out in two stages according to the method of Marshall and Richens [9]. First, the digitized data from each target displacement were processed to locate saccades. Each saccade was then analysed to extract the size of the saccade in degrees and the peak saccade velocity (fig. 3). Few saccades are completely accurate and so the size of the saccade may be greater (overshoot) or less (undershoot) than the target displacement. Because peak velocity is determined by the size of the saccade and not the size of the target displacement, it is necessary to model the velocity–saccade size relationship and calculate the velocity achieved for a fixed saccade size. This was done by fitting a quadratic equation to the peak velocity data using the calculated saccade angle as the independent variable. The influence of outliers in the data was minimized by carrying out the fitting procedure twice and weighing the second fit with the inverse of the square of the residuals from the first fit. The value for peak velocity for 30°, 35° and 40° saccades was calculated by interpolation. The values at 30° were chosen for this study as peak saccadic velocity reaches a maximum at saccades of approximate 30° of angular movement [10].

Each study day consisted of three treatment sessions separated by 30-min rest periods. Each session comprised a 10-min baseline breathing air, 25 min of low concentrations of test gas and 25 min of high concentrations of the test gas—or a complete session breathing air. The low and high concentrations of test gases were 5% and 10% MAC (5% and 10% nitrous oxide; 0.06% and 0.12% isoflurane). The order in which the

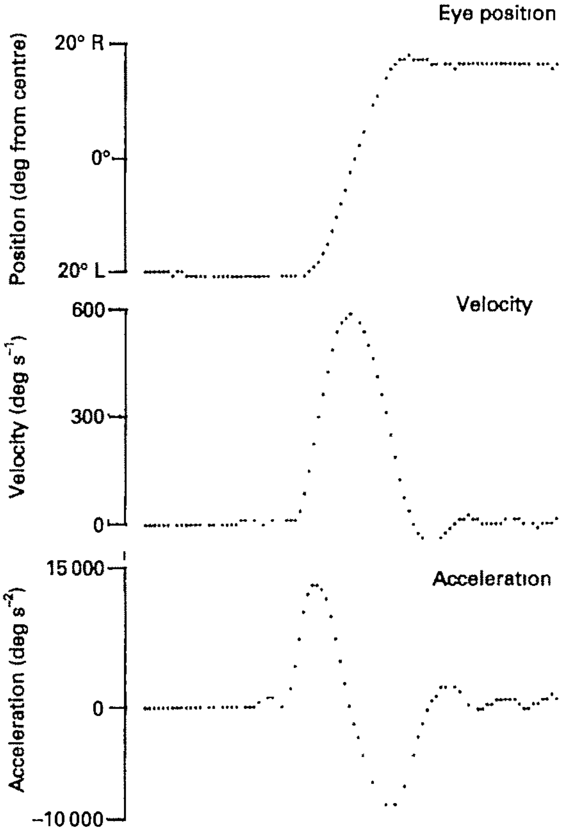

FIG. 3. Computer printout of a portion of the computer-sampled data for a single saccade. The top panel shows the digitized electro-oculograph (EOG) data which measures eye position. Each symbol represents the magnitude of the EOG at the instant of sampling. The data on the lower two panels are derived from the digitized EOG by numerical differentiation. The middle panel shows the first derivative, which gives the eye velocity at each instant of sampling. The lower panel is the second derivative of the EOG, which gives the acceleration of the eyes at each sampled point.

three test gases were administered (each on a different day) was permuted (six different sequences) and which subject had which sequence was randomized by having each subject at his first session select one of six pieces of paper (without encouragement), each containing a different one of the six possible sequences.

The saccade data were normalized for differences in basal peak velocity by subtracting the mean baseline peak saccade velocity for each treatment session from the other values obtained during that session. The difference data were analysed by two-way ANOVA (main factors subject and treatment) followed by Student's Neuman–Kuels multiple range test to identify significant differences. A significant difference was taken as $P < 0.05$, and a highly significant difference as $P < 0.01$.

Subjective assessments

These were made at the end of each treatment by asking for any appreciation of odour and feelings of tiredness, drowsiness, sleepiness and nausea.

RESULTS

The mean values of peak saccadic velocity at 30° from the three treatments are shown in figure 4. No significant difference was found between air and either 5% or 10% nitrous oxide. However, significant differences ($P < 0.05$) were seen at 15 and 25 min after 0.06% isoflurane compared with air and highly significant differences ($P < 0.01$) at 5, 15 and 25 min after 0.12% isoflurane compared with air and nitrous oxide.

The subjective assessment of the appreciation of odour, the feeling of nausea and the degree of sedation with each treatment is shown in table I.

DISCUSSION

The experiments were planned in the expectation that equi-MAC concentrations of different inhalation agents would have broadly similar effects on peak saccadic velocity; at the very least we expected an effect with a threshold concentration for detection and one for which some dose–effect relationship might be measured. In the event, a dose–effect relationship clearly exists for isoflurane; however, it was not anticipated that nitrous oxide would be indistinguishable from air at equi-MAC concentrations which produced quite marked effects with isoflurane.

In another study, patients sedated with 33% MAC of nitrous oxide and isoflurane produced the same assessment of sedation, drowsiness and sleepiness, although isoflurane produced complete amnesia for recall of events during the surgical procedure and nitrous oxide did not [11]. Likewise, inspired concentrations of 25% nitrous oxide and 0.4% isoflurane produced statistically significant effects compared with control on psychomotor performance as assessed by choice reaction time, visual analogue scales, tapping test and mathematical problems, although the effects were significantly greater with isoflurane than with nitrous oxide [12]. Cook and others [13, 14] demonstrated significant dose-dependent quali-

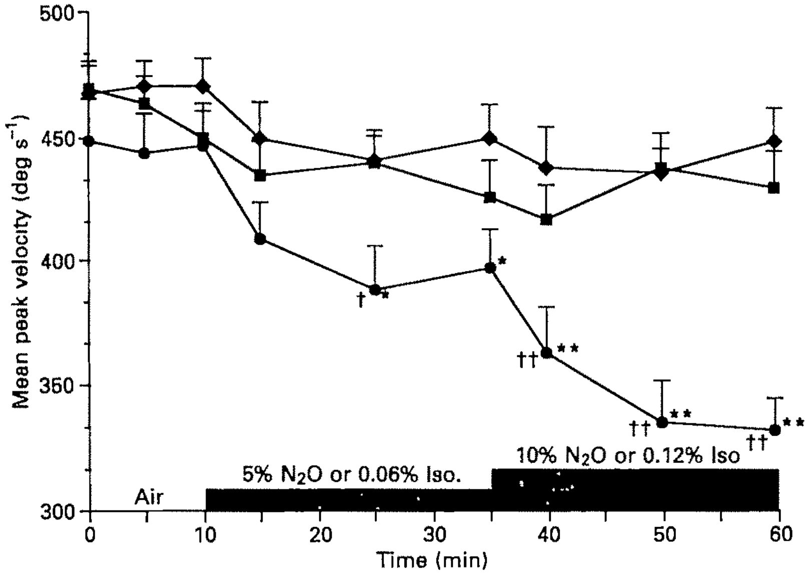

FIG. 4. Mean saccadic peak velocity (SEM) before and during inhalation of air (◆), nitrous oxide (■) and isoflurane (●). $^{*}P < 0.05$; $^{**}P < 0.01$, isoflurane compared with air; $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$, isoflurane compared with nitrous oxide.

TABLE I. *Subjects' assessments following each treatment*

	Air	N_2O	Isoflurane
Odour			
Absent	6	3	3
Present	0	3	3
Tiredness	1	4	3
Drowsiness	0	1	2
Sleepiness	1	0	1
Nausea	0	1	0

tatively similar impairment of mental function and manual dexterity at subanaesthetic concentrations of halothane, enflurane and nitrous oxide (about 13% and 27% of MAC).

Thus, although others have failed to detect differences between equi-MAC subanaesthetic concentrations of inhaled agents, this has always been using higher concentrations and, even then, there has been a suggestion of lesser effects with nitrous oxide.

Magnusson and colleagues [6] have reported significant depression of peak saccade velocity at inhaled concentrations of 14%, 21% and 28%. However, their experiments differ from ours in so many aspects that it is difficult to make direct comparisons. All of their concentrations were greater than ours. They used voluntary rather than directed saccades. Also, the angular displacements used were very large (60°) and unphysiological. More importantly, they did not control against changes in peak velocity over the course of the treatments.

Our results indicate that equi-MAC concentrations of nitrous oxide and isoflurane are not equipotent in terms of their ability to reduce peak saccadic velocity, although there did not seem to be much difference between the agents by subjective assessment. We have checked carefully the method of gas sampling and gas analysis and are confident that they are accurate. The end-tidal concentration has a predictable relationship to brain tension which is fairly close with agents of low solubility [15]. It would thus seem that it may be too simplistic to assume that equi-MAC concentrations have equivalent actions throughout the CNS.

This study could be interpreted as suggesting that the slopes of the concentration–response relationships for the two agents are not parallel, which in turn suggest that they may have different mechanisms of action in producing MAC. It may be, however, that the concentration–response relationship for effects on eye movements is not the same as that for MAC and that the eye movement test is discriminating a difference between the gases that MAC does not.

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SUBHYPNOTIC DOSES OF THIOPENTONE AND PROPOFOL CAUSE ANALGESIA TO EXPERIMENTALLY INDUCED ACUTE PAIN

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P. SCHULTZ, M. S. KRISTENSEN AND P. BJERRING

SUMMARY

Subhypnotic doses of thiopentone are considered to have a hyperalgesic effect, while propofol has a hypoalgesic effect. We investigated the effect of these drugs on the nociceptive system by measuring the pain threshold to laser stimulation and the pain evoked potential (power and latency). Nineteen patients (ASA group I) participated. Twelve patients received thiopentone 0.5 mg kg^{-1} and propofol 0.25 mg kg^{-1} in random order separated by an interval of 14 h, and seven patients received saline. Immediately after the injection of both agents, the pain threshold was increased significantly ($P < 0.001$) and the amplitude of the evoked potential was reduced significantly ($P < 0.05$), while the latency of the evoked potential remained constant. It is concluded that, in subhypnotic doses, both thiopentone and propofol decrease the acute pain evoked by argon laser stimulation.

KEY WORDS

Anaesthetics, intravenous · propofol, thiopentone Monitoring: evoked potentials. Pain: experimental

It has been suggested that subhypnotic doses of thiopentone have a hyperalgesic effect on somatic pain [1, 2]. A later study [3] confirmed that thiopentone in subhypnotic doses (0.5–1.5 mg kg^{-1}) increased the sensitivity to somatic pain, while propofol 0.25–0.5 mg kg^{-1} reduced sensitivity. In these studies, somatic pain was induced by a tibial pressure algesimeter [1, 4]. Both drugs are used widely and it is therefore important to clarify whether these drugs have a hyper- or hypoalgesic effect.

New techniques for assessment of somatic pain have been developed since Clutton-Brock introduced the pressure algesimeter [4]. Laser stimulation has been suggested as a reliable and quantitative technique to stimulate the cutaneous nociceptors without concurrent activation of mechanosensitive receptors [5] and for evaluating the potency of various analgesics [6–8].

In the present study we applied this technique to assess the effects of subhypnotic doses of thiopentone and propofol on the pain threshold and pain evoked potentials to laser stimulation.

PATIENTS AND METHODS

Twelve non-premedicated, ASA I patients (eight female) participated in the investigation. Median age was 33 (range 21–49) yr and median weight 64 (44–86) kg. Seven non-premedicated patients (one female) participated as controls; their median age was 33 (29–35) yr and median weight 80 (52–85) kg. Informed consent was obtained in agreement with the Helsinki II declaration, and the investigation was approved by the local Ethics Committee. During the experiment the patients rested comfortably and wore goggles to protect against the laser light.

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Laser stimulation

The output from an argon laser (Spectra Physics, 168) was transmitted to the skin via a quartz fibre. Output power could be adjusted from 50 mW to 3.5 W. The argon light wavelengths were 488 nm (blue) and 515 nm (green); the beam was composed of both wavelengths, and the energy distribution was 33% and 66%, respectively. This distribution remained constant for laser intensities greater than 50 mW. An external laser power meter (Ophir, Israel) was used to measure the power dissipated from the fibre. A continuous, low energy beam (50 mW) from the argon laser was used to visualize the stimulation site. To keep the energy density of the beam low, a 200-ms stimulus duration and a 3-mm laser beam diameter were used; these stimulus parameters have been found adequate to elicit distinct pain without causing superficial burn lesions [5]. The greatest laser intensity applied to the skin was 3 W, because intensities greater than this may cause minor, superficial burns. The laser stimulus was applied to the dorsal part of the right hand within a target area of 1 × 3 cm^2. The target area was encircled by ink to ensure that the same area was used for consecutive stimulations. Repeated stimulations at identical points within this area were avoided by dividing the area into small sectors which were stimulated sequentially.

Pain thresholds to laser stimuli

The pain threshold to laser stimulation was defined as the lowest energy eliciting a distinct, sharp pinprick sensation. The thresholds were calculated as a mean of three ascending and three descending series of stimulation [5]. Initially the threshold was determined five times.

Recording of pain related potentials

The pain threshold is defined as a change in modality, but the intensity of the pain perceived cannot be evaluated by the threshold alone. Pain evoked potentials include this dimension, because the amplitude or power of the potential reflects the intensity of the pain perceived.

The potentials were recorded with a platinum needle electrode (Disa 25C04) inserted over the vertex of the scalp with reference to the linked earlobes. The EEG was amplified, filtered by a second order filter (0.5–12 Hz) and sampled by a computer. Pain evoked potentials recorded over the vertex are large, and 16–24 potentials were averaged in order to obtain a sufficient signal-to-noise ratio. The major complex of the evoked potentials had a latency of approximately 300 ms (fig. 1). This potential is often characterized as a vertex potential. The amplitude or power of this complex is within a range of intensities found to correlate with the intensity of the pain stimulus, and is thus a quantitative technique for assessment of experimentally induced pain [9]. The latency of the complex provides information on velocity of conduction along the peripheral and central pain pathways.

The laser intensity used for stimulation corresponded to strong pain. This stimulus intensity was maintained constant throughout the experiment. The intervals between stimuli were randomized with a mean of 15 s (10–20 s). To avoid visual and auditory interference, volunteers wore protective goggles and earphones. The power (0.5–7.5 Hz) of the pain-evoked response 200–700 ms after stimulation was calculated and used for quantification [9]. This measurement has been shown previously to be sensitive to changes in the intensity of pain perceived [9].

Procedure

I.v. subhypnotic doses of propofol (0.25 mg kg^{-1}, 10 mg ml^{-1}) or thiopentone (0.5 mg kg^{-1}, 2.5 mg ml^{-1}) were injected in random order. The patients and investigator were blinded to the injections, the duration of which was 10–15 s, whatever the volume. The intervals between injections were 13–15 h. The pain threshold was measured before and every 1 min after injection for 10 min. In eight of the patients the evoked potentials were registered before and 15 min after the injections. The group of seven controls were given i.v. saline 10 ml and pain thresholds were determined at the same times as in the thiopentone and propofol groups. Evoked potentials were measured before and 15 min after injection.

The patients were asked to report any side effects.

Statistical analysis

Wilcoxon's test (signed rank sum) and Student's *t* test were used for statistical evaluation of the results. Statistical significance was accepted at a 5% level.

RESULTS

Side effects

No side effects were noted, but the patients generally felt more drowsy after thiopentone than

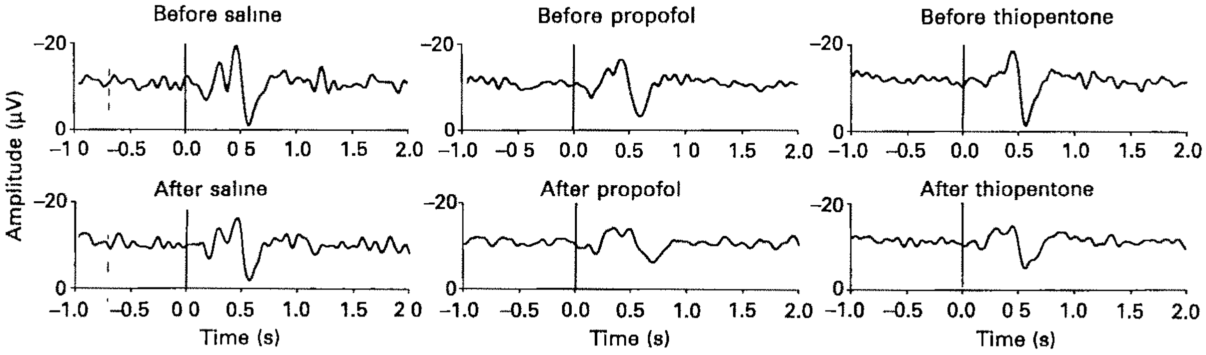

FIG. 1. Pain-evoked potentials recorded before and 15 min after saline 10 ml and subhypnotic doses of thiopentone (0.5 mg kg^{-1}) and propofol (0.25 mg kg^{-1}). The power (0.5–7.5 Hz) of the potential in the 200–700 ms post-stimulus interval was used for quantification.

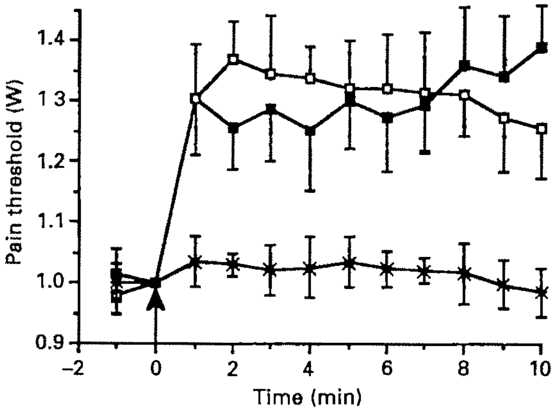

FIG. 2. Mean (SEM) pain thresholds determined before and every 1 min for 10 min after saline 10 ml (x) and subhypnotic doses of thiopentone 0.5 mg kg^{-1} (□) and propofol 0.25 mg kg^{-1} (■) ($n = 12$).

after propofol. Drowsiness occurred 0.5–1 min after injection.

Pain threshold

In the control group no significant changes were observed (fig. 2). The coefficient of variance was 4.2%.

After injection of thiopentone 0.5 mg kg^{-1} the pain threshold increased rapidly ($P < 0.001$) to approximately 1.5 times the initial value (fig. 2). The peak value was reached 2 min after injection. The pain threshold declined slowly for the next 10 min, but was still increased significantly ($P < 0.001$) after 10 min.

The pain threshold increased gradually up to 10 min after injection of propofol 0.25 mg kg^{-1}. After 10 min the pain threshold was increased significantly ($P < 0.001$), to 1.35 times the initial value.

Evoked potentials

The power of the evoked potentials measured from the control group decreased ($P < 0.05$) by 11 (SEM 5)%.

Fifteen minutes after thiopentone, the pain-related evoked potential was decreased ($P < 0.05$) by 15 (4)% compared with the initial value and with the placebo group. The power of the evoked potential after propofol was reduced ($P < 0.001$) by 17 (5)% compared with baseline and placebo.

The latency of the major negative complex remained constant under all conditions (mean 364 (SEM 40) ms), indicating no effect of the drugs on velocity of conduction along the pain pathways.

DISCUSSION

One of the main problems in pain research is measurement of pain. One method used to elicit pain is the algesimeter, with which a metal disc (9.2 mm) is pressed against the anterior part of the tibia with increasing pressure from 454 to 7264 g. This method was introduced by Clutton-Brock [4] and was used by Dundee [2] to show that subhypnotic doses of thiopentone have a hyperalgesic effect. Briggs and co-workers [3] compared the effects of subhypnotic doses of thiopentone and propofol and found the latter to have a hypoalgesic action. Robson, Davenport and Sugiyama [10] showed that, although thiopentone decreased the pain threshold as measured by tibial pressure, it increased the pain threshold as measured by thermal stimulation from a heated platinum wire pressed on the thenar eminence. This is in agreement with our results indicating that the pain from tibial pressure differs from pain elicited by heat stimulation. The obvious explanation is that the algesimeter stimulates not only nociceptive receptors, but also those for touch and pressure. The argon laser pulses stimulate predominantly the Aδ innervated nociceptors [5, 9] and facilitate the study of the hypo/hyperalgesic effects of different substances.

While the assessment of the pain threshold reflects mainly changes in sensitivity to the stimulus, the pain-evoked potential also encompasses perception of the stimulus and changes in velocity of conduction along pain pathways.

Clutton-Brock [11] explained the hyperalgesic effect of thiopentone (and several other anaesthetics) by the inhibition of an ascending, reticulo-cortical inhibitory system facilitating the perception or transmission of pain. The evoked potentials showed a decrease in amplitude after both thiopentone and propofol, but no changes in velocity of conduction along the pain pathway.

The decrease in amplitude of the pain-evoked potential for the control group is a general feature for this class of brain potentials [9]. The potential evoked by pain is not fundamentally different from the so called vertex potentials evoked by auditory and visual stimuli. These potentials also decrease by 10–20% between subsequent recordings, probably because of changes in attention. Attention and distraction are known to augmentate and reduce, respectively, the amplitude of the vertex potential. As attention is difficult to control, the potential inevitable decreases for repetitive recordings.

In conclusion, both thiopentone and propofol increased the pain threshold and reduced the amplitude of the evoked potential to acute laser induced pain. The latency of the potential remained constant. We cannot confirm the previous findings of a hyperalgesic effect of thiopentone.

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PAIN ON I.V. INJECTION OF SOME ANAESTHETIC AGENTS IS EVOKED BY THE UNPHYSIOLOGICAL OSMOLALITY OR pH OF THEIR FORMULATIONS

W. KLEMENT AND J. O. ARNDT

SUMMARY

We have studied the intensity and time-course of pain during and after injection into an isolated vein segment in seven normal subjects of saline or glucose of different osmolalities (0–6 osmol kg^{-1}) or pH (2–13). Pain scores were recorded continuously by a modified visual analogue scale apparatus. With osmolar stimulation, pain occurred at 1.0 osmol kg^{-1} during perfusion and 3.0 osmol kg^{-1} with rapid injection and increased with osmolar concentration of both saline and glucose solutions. Acidic and alkaline solutions evoked pain at a pH value < 4 or > 11. We conclude that pain on i.v. injection of some sedative and hypnotic drugs is likely to be caused by formulations of extremely unphysiological osmolalities or pH values.

KEY WORDS

Anaesthetics, intravenous Complications · pain on injection, pH, osmolality.

The principal stimulus that evokes pain on i.v. injection of some agents used as supplements for anaesthesia is still unknown. The importance of osmolality is suggested by the reported venous sequelae following x-ray phlebography. The incidence of pain on injection and thrombotic complications appear to be lower with x-ray contrast media of low osmolality [1, 2]. Although the relationship between i.v. osmolality and pain intensity has not been examined systematically, the incidence of pain seems to increase at osmolalities greater than 1 osmol kg^{-1}.

In view of these findings, it is surprising that little attention has been paid to the fact that a number of anaesthetic agents evoking pain on injection are used in formulations of extremely unphysiological osmolality. For example, diazepam [3, 4] and etomidate [5] are dissolved in solutions of osmolalities more than 10-fold that of blood [6]. Finally, painful injections are reported for agents such as methohexitone and thiopentone [7], vecuronium and nalbuphine, although they are used in formulations of less than 0.8 osmol kg^{-1}. According to our own measurements, the formulations of these drugs have an unphysiological pH. Methohexitone and thiopentone are rather alkaline (pH 11.5–12.2, depending on the solvent) and vecuronium and nalbuphine are acidic (pH 4.1 and pH 3.5, respectively).

To test the hypothesis that the osmolality or pH of anaesthetic drug formulations is the principal stimulus causing pain, we have administered solutions of varying osmolality or pH into a segment of a dorsal hand vein. We were particularly interested to identify the threshold concentrations at which pain occurred.

SUBJECTS AND METHODS

Seven healthy subjects (authors and medical students) volunteered and consented to this study, which was approved by the Committee on Medical Ethics of the University of Düsseldorf. Experiments started at 09:00 with the subjects sitting comfortably semi-recumbent at a thermoneutral room temperature of 25 °C.

A vein segment, free of side branches, between two valves was identified on the dorsum of the non-dominant hand. Two Teflon cannulae (Venflon 2, Viggo AB) were inserted from distant proximal and distal puncture sites (fig. 1), thus permitting the vein segment to be isolated from the systemic circulation by external occluders.

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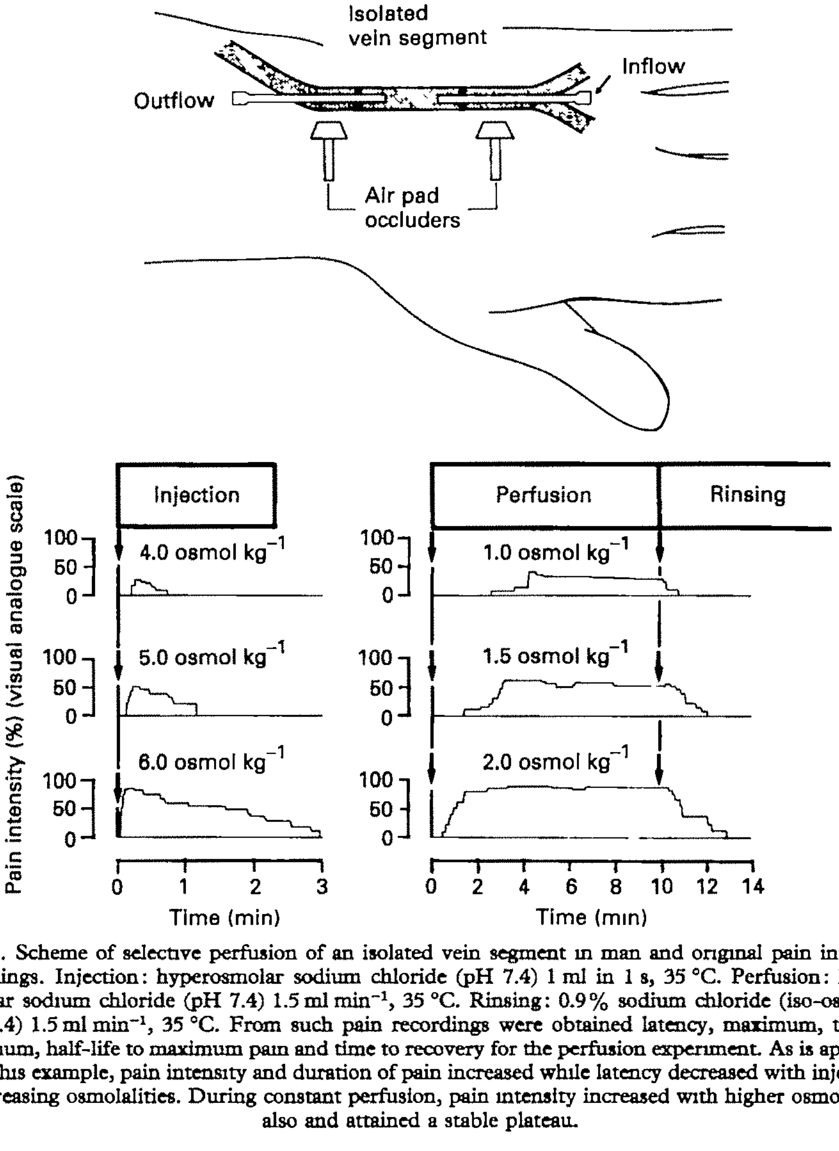

FIG. 1. Scheme of selective perfusion of an isolated vein segment in man and original pain intensity recordings. Injection: hyperosmolar sodium chloride (pH 7.4) 1 ml in 1 s, 35 °C. Perfusion: hyperosmolar sodium chloride (pH 7.4) 1.5 ml min^{-1}, 35 °C. Rinsing: 0.9% sodium chloride (iso-osmotic) (pH 7.4) 1.5 ml min^{-1}, 35 °C. From such pain recordings were obtained latency, maximum, time to maximum, half-life to maximum pain and time to recovery for the perfusion experiment. As is apparent from this example, pain intensity and duration of pain increased while latency decreased with injections of increasing osmolalities. During constant perfusion, pain intensity increased with higher osmolalities also and attained a stable plateau.

With the cannulae in place, the hand was raised on a cushioned holder above heart level so that the hand veins were almost empty at all times, in order to minimize dilution or buffering of the test solutions by blood.

Subjects rated pain intensity on a modified visual analogue scale with the help of an apparatus of our own design. A handle, connected to a linear potentiometer, could be moved over a distance of 80 mm from the left (no pain) to the right (maximally tolerable pain), yielding a voltage proportional to the rated pain intensity between 0 (no pain) and 100% (tolerance maximum). The voltage was recorded continuously on a Gould TA 500 Polygraph so that it was possible to follow not only the intensity, but also the time-course of the evoked pain (fig. 1).

Hyperosmolar saline and glucose solutions were prepared at concentrations of 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 osmol kg^{-1} at constant pH (7.4). Saline solutions of pH between 2–13 were prepared by adding sodium hydroxide or hydrochloric acid. The osmolality was constant (0.3 osmol kg^{-1}) at each pH.

For i.v. block, procaine concentrations between 0.1 and 1.0% ($3.7–36.7 \times 10^{-3}$ mol litre^{-1}) in steps of 0.2% were prepared with Tyrode's solution at osmolar concentrations between 0.29 and 0.30 osmol kg^{-1} at pH 7.4.

All solutions were given i.v. at 35 °C (the temperature of blood in cutaneous hand veins).

Each subject was studied twice on different days separated by 1–2 weeks. On one day the vein was exposed to varying osmolalities, and on the other to varying pH. To avoid the influence of possible long-term tissue alteration at the sensory structures of the vein wall, venous segments were not used twice.

The collapsed vein segment was perfused continuously with saline (pH 7.4, 0.3 osmol kg^{-1}, 35 °C, rate 3 ml min^{-1}) in order to simulate injections into a normally patent vein. In each subject, the study sequence was as follows: during a control period of 10 min, the vein segment was perfused continuously with iso-osmotic saline (3 ml min^{-1}); during saline perfusion, 1 ml of the test solutions of different osmolality or pH was injected at random within 1 s. Each concentration was administered twice in any experiment.

With the vein segment separated from the systemic circulation by external air pad occluders, the isolated segment was perfused continuously at constant osmolality of 1.0, 1.5 and 2.0 osmol kg^{-1} at 1.5 ml min^{-1} for 10 min each, and thereafter rinsed with iso-osmotic saline.

The perfusion experiment was repeated on a separate day using glucose solution in equal osmolar concentrations in three subjects.

Isolation of the vein segment during the experiment was confirmed by the absence of erythrocytes in the effluent perfusate and by identical osmolalities of the in- and outflowing solution.

After the test injections were completed, the isolated vein segment was perfused continuously with procaine. Starting with 0.1 and 0.2%, the procaine concentrations were increased in steps of 0.2% and maintained at a given concentration for 10 min each. The subjects' maximal pain rating to a painful stimulus of constant osmolality and volume was evaluated before procaine and during the last 1 min of perfusion at each given concentration of procaine. Thereafter, the vein segment was rinsed with saline until pain intensity reached control values.

Latency, maximum pain intensity and duration were evaluated from the recordings (fig. 1). Concentration–effect curves were plotted for each subject by relating the osmolality or pH to the subjects' maximum pain intensity in injection and in perfusion experiments.

The latencies (time from exposure to drug to occurrence of pain), durations and times to maximum evoked pain sensation were tabulated as means and ranges. For the perfusion experiments, the half-lives to maximum and to recovery (time from the start of sensation to 50% of maximum pain and time from the start of rinsing to 50% of recovery, respectively) were tabulated also.

RESULTS

Pain occurred earlier as the osmolalities increased in both the injection and the perfusion experiment. With the injections, pain was transient and subsided within 2–5 min. In contrast, during

TABLE I. *Time course (mean (range)) of pain following injections of saline with varying osmolality and pH. Data from seven subjects with hyperosmolar and three subjects with acidic and alkaline stimulation*

	Pain		
	Latency (s)	Duration (s)	Time to maximum (s)
Hyperosmolar saline			
Osmolality (osmol litre^{-1})			
3.0	13	31	22
	(12–15)	(0–51)	(17–33)
4.0	10	50	28
	(7–12)	(21–60)	(18–39)
5.0	7	74	32
	(5–9)	(32–101)	(16–40)
6.0	5	135	34
	(4–6)	(52–262)	(11–59)
Acid saline			
pH			
3.5	8	15	14
	(7–14)	(0–23)	(12–16)
3 0	6	23	14
	(5–9)	(16–28)	(8–18)
2.5	5	45	14
	(4–9)	(32–56)	(11–19)
2 0	4	68	12
	(3–6)	(55–82)	(9–16)
Alkaline saline			
pH			
11.5	9	11	13
	(7–12)	(0–15)	(9–16)
12 0	6	65	18
	(4–8)	(15–137)	(9–29)
12 5	4	110	9
	(3–6)	(30–226)	(5–15)
12 0	3	282	7
	(3–5)	(252–312)	(4–10)

TABLE II. *Time-course (mean (range)) of pain during hyperosmolar saline perfusion. Data from seven subjects*

Osmolality (osmol litre^{-1})	Pain during perfusion and rinsing			
	Latency (s)	Time to maximum (s)	Half-life (s)	
			To maximum	To recovery
1.0	223 (75–378)	405 (252–528)	106 (42–153)	32 (8–48)
1.5	95 (36–168)	304 (189–414)	71 (42–96)	41 (12–78)
2.0	30 (6–78)	195 (96–363)	69 (24–180)	82 (15–180)

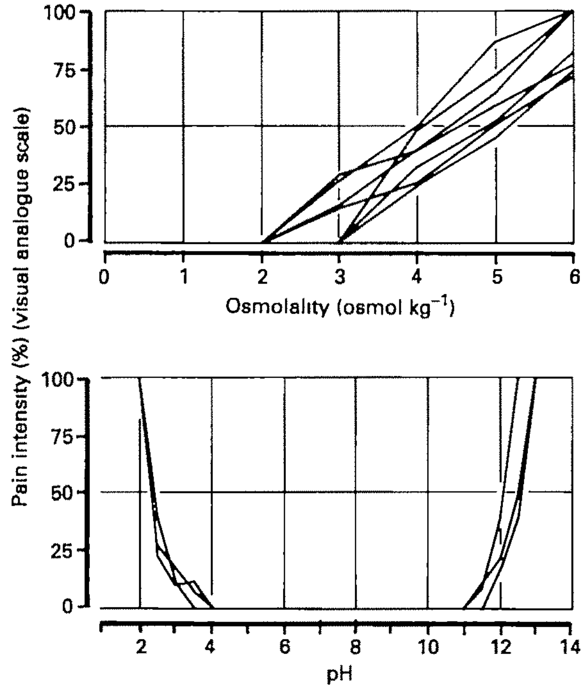

FIG. 2 Pain intensity–concentration relationships with injections of varying osmolalities or pH. Data from all seven subjects with osmolar stimulation (above) and from three subjects exposed to alkaline and acid saline (below). Note that, above the individual thresholds, pain intensity increased only with increasing osmolalities, but with both increasing and decreasing pH.

constant perfusion, pain intensity at a given concentration was maintained until the pain-evoking solution was washed away.

For injections of varying osmolality and pH, the temporal variations between stimulus application and pain are summarized in table I. The latencies decreased from 13 s at the least to 5 s at the greatest osmolality, while the times to maximum pain did not change with stimulus strength. The duration of pain varied markedly between subjects (e.g. 52–262 s with the injection of 6.0 osmol kg^{-1}), but increased with greater osmolality in each subject.

In the case of the pH stimulus, pain lasted at least 250 s after injection of alkaline solution (pH 13)—much longer than after the injection of acidic saline (55–82 s). The latencies decreased with both acidity (from 8 to 4 s) and the basicity of the injectate (from 9 to 3 s).

The perfusion experiments (table II) revealed a close relationship between stimulus strength and the time-course of pain as both the latencies and times to maximum pain decreased with increasing osmolality. The half-lives to maximum pain and to recovery reached similar values with the greatest osmolality.

Injections with hyperosmolar saline evoked pain whenever the osmolality exceeded 3.0 osmol kg^{-1}. As shown by each subject's concentration–effect relationship in figure 2, pain intensity increased almost linearly with the osmolality of the test solution. The minimal osmolality that just evoked pain (pain threshold) was 3.0 in four subjects and 4.0 osmol kg^{-1} in the remaining three. Maximum pain occurred at approximately 6.0 osmol kg^{-1}, with which pain intensities ranged between 72 and 100 % (100 % = tolerance maximum) of the intensity scale, while two subjects rated their pain as intolerable. It should be noted that hypo-osmolar solution (distilled water) did not evoke pain.

Solutions of both high acidity and high alkalinity evoked pain at the extreme ends of the pH

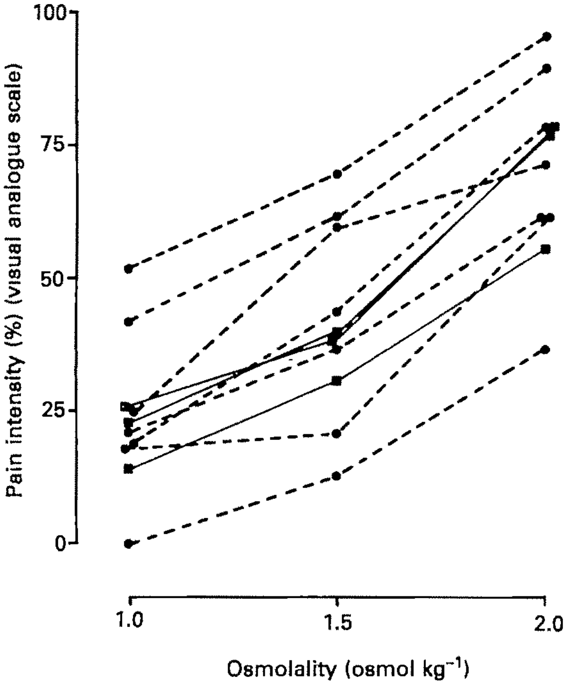

FIG. 3 Pain intensity–osmolality relationships during continuous perfusion. Saline was used in all seven subjects (●) and additionally glucose (■) in three of the subjects. Note that above threshold pain intensity always increased with increasing osmolality. Note also the congruency of pain intensity–concentration curves for saline and glucose.

scale ($pH \leqslant 4$ and $pH \geqslant 11$). The intensity of pain increased as the pH increased to more than 11 or decreased to less than 4 (fig. 2). Tolerance maxima were reached at a pH of 2 and 13, respectively. The subjects rated the pain as intolerable with three of six injections.

Because of severe sequelae described below, the pH effects were studied in three subjects and with injections only.

Constant perfusion of the isolated vein segment with hyperosmolar concentrations evoked pain at lower thresholds (1.0 osmol kg^{-1}) than with injections (3.0 osmol kg^{-1}) (fig. 3). Concentrations less than 1.0 osmol kg^{-1} did not cause pain even when the perfusion time lasted 10 min. Pain intensity increased almost linearly with osmolality in the range 1.0–2.0 osmol kg^{-1}, but differed markedly between subjects. No difference occurred in pain intensity–concentration relationships between saline and glucose.

With increasing i.v. concentrations of procaine, pain intensity decreased, even though the stimulus strength of the injectate (6.0 osmol kg^{-1}) was the same as before local anaesthesia. Pain on injection disappeared completely at an i.v. concentration between 0.4% (14.7×10^{-3} mol litre^{-1}) and 0.8% (29.4×10^{-3} mol litre^{-1}), in five of the seven subjects at 0.6% (22×10^{-3} mol litre^{-1}) and recurred within 10 min during rinsing. It should be stressed that i.v. administration of procaine did not block sensation of the overlying skin as tested by mechanical (touch, pinprick) and thermal (warm, cold) stimuli.

All subjects described the evoked pain as dull, burning, oppressive and highly unpleasant. Low intensity pain was localized by the subjects at the site of injection of the isolated vein segment but, with intensities greater than 70% of the tolerance maximum, pain extended from the site of injection to the whole dorsum of the hand, extensive areas of the forearm, and sometimes also the palm of the hand.

Every subject suffered small to moderately painful venous sequelae up to 24 h after the experiment, characterized by increased sensitivity to touch and by cutaneous flush. In five of the seven subjects, the veins became indurated for up to 4 weeks, but thereafter regained normal appearance and function.

After injection of acidic and alkaline solutions, perivenous oedema developed immediately and was followed by a thrombophlebitis for up to 3 weeks. These sequelae were not confined to the perfused vein segment, but spread over the dorsum of the hand and parts of the forearm. For ethical reasons, we refrained from further experiments on pH effects, in particular those with constant perfusion.

DISCUSSION

Both the osmolar concentration and pH of solutions brought into contact with the intact intima of a superficial hand vein were factors determining the evocation of pain.

We believe our methods ensured that the intima, the only layer between blood and the subendothelially-located receptive endings [8], was intact, that the dilution and buffering of the test solutions by blood was avoided or at least minimized and that, during the procaine experiments, procaine did not enter the systemic circulation. These precautionary aims were met by injecting the test solution into a collapsed vein segment devoid of branches via a smooth Teflon cannula placed into that segment from distant puncture sites that could not be reached by the solutions. The proximal cannula, used as the inflow path, prevented blood from entering the segment; the valves prevented retrograde outflow. When the test solutions were injected (1 ml within 1 s), the dilution by the continuous infusion of saline 3 ml min^{-1} and by the remaining blood flow was comparable to the clinical situation when drugs are injected into an infusion. In this case, the exact i.v. osmolality and pH were uncertain. However, the i.v. concentration was certainly constant during perfusion, as the measured osmolality of the effluent perfusate differed by not more than 3% of the inflow solution.

Continuous recording of the subjects' pain ratings via the modified visual analogue scale made it possible to judge both the intensity and the time-course of the evoked pain. Two observations are worthy of note. First, the same concentrations were rated as almost equally painful on repeat administration with intra-individual differences of less than 10% of the visual analogue scale. Second, at constant osmolar concentrations during perfusion, the plateau of the pain intensities did not change while the stimulus strength was maintained constant for 10 min (fig. 1). This is noteworthy because cutaneous nociceptors are known to adapt within seconds when stimulated with constant noxious pressure or heat [9]. This observation and the fact that randomly varied concentrations gave highly repeatable results with only minimal variations in pain intensity, support our contention that subjective pain rating is a reliable and reproducible index from which to derive concentration–effect relationships.

Above the individual thresholds, pain intensity increases almost linearly up to a certain maximum. Regardless of threshold differences between the subjects, the ranges of osmolality (3.0–6.0 osmol kg^{-1}) and pH (4.0–2.0 and 11.0–13.0) which evoked pain were often less than that of commercially available drug solutions known to cause pain on injection. For example, diazepam and etomidate are used in formulations of 7.8 and 5.0 osmol kg^{-1} [6]. Pain on injection of these drugs is therefore likely to be the consequence of the extreme osmolalities and pH values of their conventional formulations.

Consistent with this view, the incidence of pain on injection was reduced to less than 1% with new emulsion formulations of diazepam and etomidate [3, 7, 10] which have osmolalities near that of blood [6].

It is worthy of note that the principal pain-evoking stimulus is the osmolar concentration rather than the ionic strength of the injectate. This is shown by the pain intensity–concentration relationships for both hyperosmolar saline (strong electrolyte, ionic dissociation near 100%) and glucose (weak electrolyte, ionic dissociation near 0%) in figure 3.

During constant perfusion of vascularly isolated vein segments, pain occurred and attained its maximum more quickly and lasted longer during the rinsing period as the osmolar concentrations increased. Also, at a given concentration, pain intensity did not change with time, but disappeared within 3 min during rinsing. Thus, in the absence of adaptation, pain depends on the osmolar concentration present in a vein at a given time, which in turn depends on the volume in and the flow of blood through this vein. The highly variable incidence of painful injections reported in clinical studies [3–5, 7] and its occurrence in particular with injections into small calibre veins is therefore not unexpected. In addition, the incidence of pain on injections may be underestimated in the case of hypnotic agents because patients are likely to lose consciousness before pain can be perceived—we found latencies to perception of pain of up to 30 s (tables I, II).

As i.v. procaine abolished pain on injection completely without numbing the skin above the perfused vein, the painful sensations from veins probably originate from neuronal elements within their walls, possibly the free afferent nerve endings between the media and intima [8]. As the transduction processes at the receptor membrane are less vulnerable to pharmacological interventions than the axonal conduction process [11], it is likely that procaine blocked nerve conduction. The pain conducting axons probably belong to the myelinated Aδ group, because pain was abolished at the same concentrations of procaine (0.4–0.8%) that abolished spike activity of thinly myelinated vagal afferents of the heart [12].

In conclusion, solutions with osmolalities > 1.0 osmol kg^{-1} and pH either < 4 or > 11 evoke pain on injection into veins at the dorsum of the hand of humans. This explains the high incidence of painful injections with several drugs which are used in formulations with extremely unphysiological osmolalities or pH. Pain on injection and perhaps also thrombophlebitis can probably be avoided by diluting hyperosmolar drug formulations with distilled water or by aspirating blood for buffering into formulations with extreme pH just before injection.

ACKNOWLEDGEMENT

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DRAWOVER ANAESTHESIA AND PREOXYGENATION

D. M. LOWE AND W. McFADZEAN

SUMMARY

We have studied the efficacy of preoxygenation using the Triservice Anaesthetic Apparatus (TSA) in healthy patients and found it to be unsatisfactory. An alternative technique suitable for field use was explored. The Mapleson D system (Bain) was found to be suitable for preoxygenation with a fresh gas flow of only 4 litre of oxygen per minute. In a randomized study using only 4 litre of oxygen per minute for 3 min, the Bain system was found to be superior to the TSA.

KEY WORDS

Anaesthetic techniques: drawover, preoxygenation.

Drawover anaesthesia is used when the supply of compressed gas is restricted, for example in military environments or the third world [1]. The use of air as the main inspired gas reduces or eliminates the requirements for compressed oxygen. For some cases (emergencies, obstetrics etc.) it is still advisable to preoxygenate the patient before induction of anaesthesia. The Triservice Anaesthetic Apparatus (TSA) [2] is a compact, lightweight, drawover anaesthetic system which has been adopted by the British armed services for field use and is commercially available. It offers an oxygen supplement of either 1 or 4 litre min^{-1} using the Houghtonox oxygen flow control. For preoxygenation, a flow of oxygen 4 litre for 3 min is recommended (a total of 12 litre of oxygen).

The purpose of preoxygenation is to extend the period of apnoea during induction before hypoxia occurs. In a drawover system inspired oxygen ($F\mathrm{I}_{\mathrm{O}_2}$) is related inversely to minute volume, assuming there is no wastage of oxygen (fig. 1). If the alveolar oxygen content is dependent on $F\mathrm{I}_{\mathrm{O}_2}$, the safe period of apnoea may be extended by increasing the $F\mathrm{I}_{\mathrm{O}_2}$. Pulse oximetry enables this period to be measured non-invasively [3].

Measuring $F\mathrm{I}_{\mathrm{O}_2}$ and $S\mathrm{p}_{\mathrm{O}_2}$ in routine use, the TSA was found to produce a low $F\mathrm{I}_{\mathrm{O}_2}$ and short periods of safe apnoea ($S\mathrm{p}_{\mathrm{O}_2} > 95\%$). Methods of improving these without increasing overall oxygen usage were sought. Following a favourable result with the Bain system in a small pilot study, a formal clinical trial was carried out.

PATIENTS AND METHODS

Ethics approval was granted for this study by the Army Medical Services Research Executive. All patients gave informed consent.

Randomized parallel group study

Thirty ASA I male patients who required intubation for a short procedure entered the study. All were healthy and had passed a basic fitness test. The patient's weight, height, age and

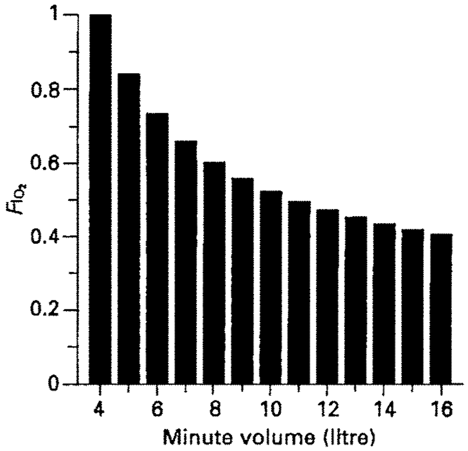

FIG. 1. $F\mathrm{I}_{\mathrm{O}_2}$ with the TSA and oxygen 4 litre min^{-1}.

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TABLE I. *Patient characteristics (mean* (SD)) *for randomized study. No significant differences between groups* (t *test, except *Behren's test, †chi-square with Yates' correction*)

	Group 1 (TSA) ($n = 15$)	Group 2 (Bain) ($n = 15$)
Height (cm)	180.4 (5.9)	181.7 (8.4)
Weight (kg)	79.4 (8.5)	75.4 (8.2)
Age (yr)*	24.7 (6.1)	22.7 (2.6)
Sp_{O_2} with air (%)	96.8 (1.4)	96.7 (0.9)
Smoking (Yes/No)†	8/7	6/9
BMI (kg m^{-2})	24.5 (3.1)	22.8 (2.4)

smoking habits were recorded before operation. Premedication was with papaveretum 15 mg and hyoscine 0.3 mg i.m. if the weight was less than 70 kg, otherwise papaveretum 20 mg and hyoscine 0.4 mg. Patients were allocated randomly to the study groups using the sealed envelope technique immediately before anaesthesia.

Group 1 ($n = 15$). Arterial oxygen saturation (Sp_{O_2}) was measured at rest, breathing air (Biox 3740, finger probe). Patients were preoxygenated using the TSA and oxygen 4 litre min^{-1} (from an anaesthetic machine) for 3 min. FI_{O_2} and end-tidal carbon dioxide concentration were measured continuously (Datex Multicap), sampling from the anglepiece of the mask. Sp_{O_2} and FI_{O_2} were measured continuously and recorded at 1, 2 and 3 min. End-tidal carbon dioxide concentration was recorded at a steady state. Anaesthesia was induced with thiopentone 5–8 mg kg^{-1} i.v. and, after loss of consciousness, suxamethonium 100 mg was given i.v. Time of apnoea was recorded from the loss of effective ventilation. A tracheal tube was inserted and left open to air. Sp_{O_2} was recorded every 20 s up to 3 min unless it decreased to 95 %. Anaesthesia was maintained with thiopentone. At 3 min or 95% saturation, the patient's lungs were ventilated with nitrous oxide and enflurane in oxygen, and the end-tidal carbon dioxide concentration of the first breath was recorded.

Group 2 ($n = 15$). These patients were treated in the same manner as those in group 1, but a Bain system attached to an anaesthetic machine was used with a fresh gas flow of oxygen 4 litre min^{-1}.

Statistical analysis

Homogeneity of variance between groups compared was examined using the F test. Between group comparisons were made using the two-sample t test (or the distribution free Mann–Whitney rank test, where departures from Normality were found). Where group variances were significantly different, the test attributable to Behrens [3] was used in place of the t test.

RESULTS

The two study groups were found to be comparable in age, weight, height, Sp_{O_2} (breathing air) and smoking habits (table I).

There was a significant difference ($P < 0.001$) in FI_{O_2} between the two groups. The TSA produced a mean FI_{O_2} of 0.59 (SD 0.09) at 3 min, compared with 0.93 (0.04) produced by the Bain system. During preoxygenation mean FE'_{CO_2} was 5.44 (0.58) kPa in the TSA group and 6.18 (0.52) kPa in the Bain group ($P < 0.001$). Mean FE'_{CO_2} for the first ventilated breath were 6.48 (0.58) kPa for the TSA group and 7.16 (0.64) kPa for the Bain group ($P < 0.01$) (table II).

The mean time to desaturate to less than 95 % in the TSA group was 107 (44.2) s and in the Bain group it was 172.7 (13.7) s ($P < 0.001$) (table III). At 1 min, three of the TSA group and none of the Bain group had desaturated and at 3 min, one of the TSA group was still saturated and 10 of the Bain group (fig. 2).

TABLE II. FI_{O_2} *and* FE'_{CO_2} *(mean* (SD)) *during preoxygenation and at first ventilated breath* (t *test, except *Behren's test*). *CI = Confidence interval*

	Group 1 (TSA)	Group 2 (Bain)	P	99 % CI for diff. between means
FI_{O_2}				
1 min	0.54 (0.11)	0.88 (0.10)	< 0.001	−0.45, −0.23
2	0.61 (0.11)	0.92 (0.05)	< 0.001*	−0.41, −0.23
3	0.59 (0.09)	0.93 (0.04)	< 0.001*	−0.42, −0.27
FE'_{CO_2} (kPa)				
Steady state	5.44 (0.58)	6.18 (0.52)	< 0.001	−1.30, −0.19
First breath	6.48 (0.67)	7.16 (0.64)	< 0.01	−1.33, −0.01

TABLE III. *Time (s) for* Sp_{O_2} *to decrease to less than 95%. CI = Confidence interval.* $^*P < 0.001$ *(Mann–Whitney rank test)*

	Mean	SD	Median	Range	99% CI for diff. between means
TSA ($n = 15$)	107.0*	44.2	109	50–180	−100.4, −30.9
Bain ($n = 15$)	172.7*	13.7	180	135–180	

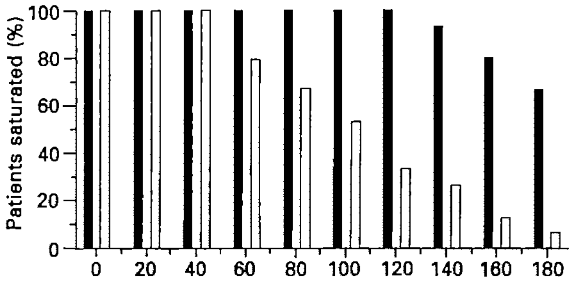

FIG. 2. Patients remaining > 95% saturated at 20-s intervals during 3 min of preoxygenation with the Bain system (■) and TSA (□).

None of the measured patient-characteristics had a significant effect on time to desaturation. Obesity has been shown to affect time to desaturation [4]; only three of the subjects were slightly obese [5]. Comparison was made between the two groups for body mass index (BMI = weight (kg)/height^2 (m)) [5]; no significant difference was found between the two groups. There was a non-significant trend towards earlier desaturation with increasing BMI in the TSA group.

DISCUSSION

The object of preoxygenation as part of a "crash induction"/rapid sequence induction is to provide time for a tracheal tube to be positioned during a safe period of apnoea. Suxamethonium takes 1 min [6] to cause satisfactory muscle relaxation; intubation and connection to the breathing circuit also take appreciable time, even in skilled hands with a normal patient. If anaesthetists are less experienced or intubation is difficult, more time is required. During the randomized study when desaturation occurred in less than 60 s ($n = 3$), intubation was not always complete.

Obesity may reduce the safe period of apnoea because of a reduction in FRC. Because of patient selection, there were not enough obese patients to draw useful conclusions from this study about the effects of obesity on preoxygenation.

In order to increase $F\text{I}_{O_2}$, a semi-closed system was used. As the gas flow was less than expected minute volume, rebreathing was inevitable but, as shown in table II, it did not result in unacceptable values of $F\text{E}'_{CO_2}$.

The choice of semi-closed system lay between a Mapleson A or D system. The Mapleson A would seem initially to be the better choice because of greater efficiency during spontaneous breathing. However, with the minute volumes of 7–14 litre encountered (inferred from $F\text{I}_{O_2}$ with the TSA) and found by others [7], and a fresh gas flow of only 4 litre, considerable rebreathing would occur with both systems.

With the Mapleson A system, there is a delay in the increase in $F\text{I}_{O_2}$ while the bag fills. If a leak occurs between the facemask and face, the gas lost is fresh gas and rebreathing occurs until the pressure in the reservoir exceeds the opening pressure of the Heidbrink valve. Attempting to use it with 4 litre of oxygen before the trial, we found it impractical, and in inexperienced hands it was unreliable.

A Mapleson D system with an efferent reservoir rapidly reaches a high $F\text{I}_{O_2}$ and if there is a leak around the mask there is no delay in restarting preoxygenation after the mask is repositioned, because the fresh gas is supplied to the patient end. In contrast, the time taken by a drawover system to reach peak $F\text{I}_{O_2}$ is dependent on the system volume distal to the oxygen inlet and the minute volume. Although this delay can be reduced by placing the oxygen inlet nearer the patient, the $F\text{I}_{O_2}$ is still limited by the oxygen supply (fig. 1). This is inherent in any drawover system.

Three or four vital capacity breaths have been suggested as an alternative method of preoxygenation [4], but this is less reliable in severe lung disease or pregnancy [8]. It is equally likely that the injured may find it less satisfactory, especially if breathing is limited by pain. After successful preoxygenation, it is essential to prevent a patient breathing air; oxygen must be supplied until apnoea occurs. In sick or injured patients, induction is likely to be slow because of slow circulation times and caution with drug doses. Systems which require high flow rates of oxygen are wasteful during the induction time. When oxygen supplies are limited by logistic or economic factors, a 3-min preoxygenation using oxygen 4 litre min^{-1} and a Bain system may achieve adequate preoxygenation efficiently. Allowing 3 min for preoxygenation also seems an easier manoeuvre for the inexperienced anaesthetist than vital capacity breaths.

In conclusion, using the TSA, low $F\text{I}_{\text{O}_2}$ limited the effect of preoxygenation in our healthy young patients. Similar results may be predicted in any other drawover system. Worse results may be expected in the old or ill. Better preoxygenation may be achieved with the same flow of oxygen using a Mapleson D system. The Bain system provides a light and convenient method of doing this if the oxygen supply from the Houghtonox valve is connected to the proximal end of the Bain system. When induction has been completed, a drawover system may be used for maintenance of anaesthesia.

ACKNOWLEDGEMENTS

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USE OF CONTINUOUS POSITIVE AIRWAY PRESSURE IN PAEDIATRIC DENTAL EXTRACTION UNDER GENERAL ANAESTHESIA

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SUMMARY

In a controlled prospective study, we studied 150 grade ASA I children undergoing outpatient dental extraction under inhalation anaesthesia with a T-piece system allocated to three equal groups: a control group (0 cm H_2O CPAP), and two study groups receiving 2.5 or 5 cm H_2O of CPAP via a nasal mask. We found that the incidence and severity of oxygen desaturation were reduced significantly in the 5-cm H_2O CPAP group.

KEY WORDS

Anaesthesia outpatient, dental. Oxygen pulse oximetry. Ventilation continuous positive pressure breathing

A decrease in arterial oxygen saturation by more than 10% has been demonstrated in children undergoing dental extraction under general anaesthesia with both inhalation and i.v. techniques of induction [1, 2]. This results predominantly from upper airway obstruction at the time of insertion of the dental prop and pack and during extractions. This obstruction may be accentuated in children of this age group by their tendency to rhinitis and hypertrophy of the adenoids and tonsils [3].

Nasal continuous positive airways pressure (CPAP) has been reported to increase oxygen saturation in the presence of measured oxygen desaturation and partial airway obstruction in adults and children, for example in obstructive sleep apnoea syndrome [4–6]. CPAP also exerts a beneficial effect on the functional residual capacity (FRC) [7–9] and the work of breathing [9].

This study was designed to measure oxygen saturation in children undergoing outpatient dental extractions, when 0, 2.5 or 5 cm H_2O of CPAP was added to a standard technique of inhalation nasal mask anaesthesia via a T-piece system.

PATIENTS AND METHODS

Following approval by the London Hospital Ethics Committee, we studied 150 children of ASA grade I, aged 1–14 yr, undergoing outpatient dental extraction under general anaesthesia. They were allocated to three groups: group A = 0 cm H_2O CPAP; group B = 2.5 cm H_2O CPAP; group C = 5 cm H_2O CPAP. The groups were studied in the sequence C, B and A and involved many anaesthetists, surgeons and trainees of varying grades, to negate the learning curve effect and to conform with our normal clinical practice. The range of ages encountered (group A 2–14 yr, group B 2–14 yr and group C 1–13 yr) reflected the occasional admission of patients at the extremes of this range during the period of study and was limited to the two patients concerned in each group (table I).

Measurement of oxygen saturation (Sp_{O_2}) commenced before anaesthesia using an Ohmeda Biox 111 BOC Health Care pulse oximeter, which has been shown to have an accuracy of ±2.4% in the 80–100% range [10]. Oxygen saturation was recorded continuously on a Gould TA 550 three-channel pen chart recorder. All patients were monitored with a Cardiorater ECG. Heart rate was recorded at 30-s intervals and incidence and duration of cardiac arrhythmias noted and recorded.

Anaesthesia was induced in patients in the

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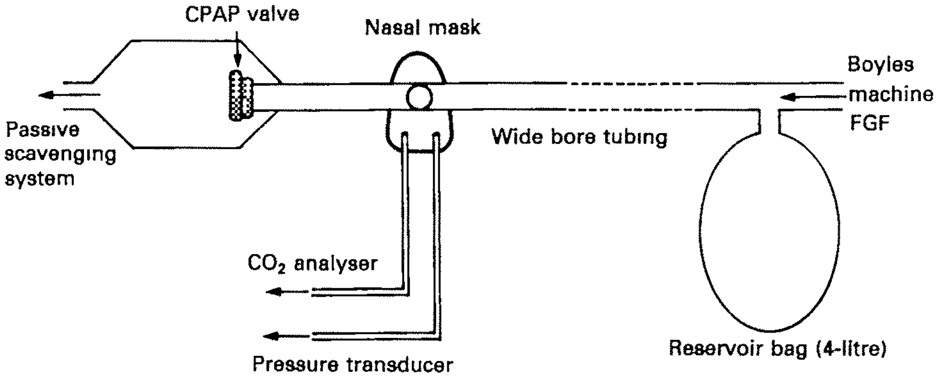

FIG. 1. Circuit diagram.

supine position via the open end of the T-piece held close to the mouth and nose, using halothane in increasing concentrations up to 5% and 66% nitrous oxide in oxygen. When judged appropriate by the anaesthetist, a nasal mask (SEFAM, France) was applied and the halothane concentration decreased to 2%. The use of a nasopharyngeal airway was left to the discretion of the anaesthetists who were of varying grades and included supervised dental students and junior trainees in anaesthesia. The grade of the person performing dental extractions (which included supervised dental students) was noted.

The T-piece system had a wide-bore inspiratory tube and 4-litre reservoir bag. A CPAP level of 0 cm, 2.5 cm or 5 cm H_2O was applied with an adjustable Heidbrink valve. The fresh gas flow used was 9 litre min^{-1} in children aged 1–7 yr and 12 litre min^{-1} in children older than 7 yr, to ensure that the reservoir bag remained almost fully distended throughout the respiratory cycle [11, 12].

The SEFAM nasal mask has two oxygen portholes which were utilized for pressure monitoring and carbon dioxide sampling (fig. 1). Carbon dioxide was measured with a Datex Normocap carbon dioxide monitor and a pen chart recorder with a sampling rate of 150 ml min^{-1}. A Gould Statham P231D pressure transducer was used to measure CPAP and, consequently, the duration of gas tight seal at the mask during the ventilatory cycle. Both the Datex Normocap and Gould Statham transducer were calibrated according to the manufacturers' instructions before each anaesthetic session. Airway pressure was recorded continuously on a Gould TA 550 three-channel pen chart recorder.

Surgery commenced when the depth of anaesthesia was judged to be adequate and key anaesthetic and surgical events were noted. Whenever desaturation in excess of 10% from baseline values occurred, surgery was interrupted until Sp_{O_2} had improved to nearer baseline values following restoration of the airway.

Statistical analysis

Parametric data were analysed using an unpaired Student's *t* test. Non-parametric 95% confidence intervals for median baseline and median least Sp_{O_2}(%) were obtained for the three groups and a Mann–Whitney *U* test used to compare baseline oxygen saturation and peroperative desaturation. The incidence of cardiac arrhythmias was compared using a chi-square test. Three-way analysis of variance was performed to compare the groups and the grades of anaesthetists and surgeons for peroperative desaturation. $P < 0.05$ was accepted as statistically significant.

RESULTS

The three groups were comparable with regard to age and numbers of teeth extracted (table I), and race (table II).

TABLE I. *Patient characteristics in groups A, B and C (T-piece system: 0, 2.5 and 5 cm H_2O of CPAP, respectively)*

	Age (yr) (mean (range))	Number of teeth extracted (mean (SEM))	*n*
Group A	6.3 (2–14)	3.9 (0.3)	50
Group B	6.5 (2–14)	3.4 (0.3)	50
Group C	5.7 (1–13)	3.4 (0.3)	50

TABLE II. *Racial distribution of patients in groups A, B and C*

	Caucasian	Asian	Negro	Negro/Caucasian
Group A	26	22	2	0
Group B	30	18	2	0
Group C	31	16	1	2

TABLE III. *Baseline and median least Sp_{O_2} (median non-parametric 95% confidence intervals) in groups A, B and C*

	Baseline Sp_{O_2} (%)	Least Sp_{O_2} (%)
Group A	98 (97–99)	96 (95–96)
Group B	99 (98–100)	96 (96–98)
Group C	99 (99–100)	98.50 (96–99)

TABLE IV. *Respiratory data (mean (SEM)).* *$P < 0.05$

	Ventilatory frequency (b.p.m.)	End-tidal CO_2 (%)
Group A	32 (1.7)	3.7 (1.1)
Group B	34 (1.4)	4.8 (0.07)*
Group C	34 (1.5)	4.6 (0.1)*

There was a significant difference between groups with regard to oxygen desaturation, the incidence and severity of which was less in the 5-cm H_2O study group compared with the control group (fig. 2, table III). Oxygen desaturation occurred mainly during the following events: induction, application of mask, insertion of the prop and pack and during dental extractions. These episodes of hypoxemia resulted predominantly from partial upper airways obstruction during these events.

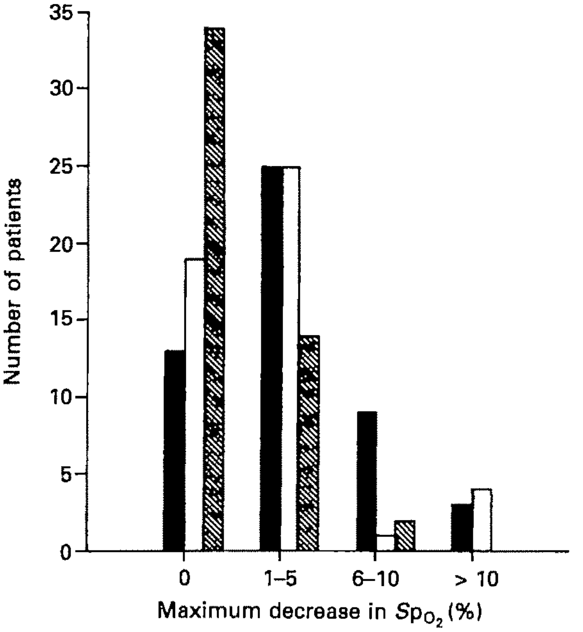

FIG. 2. Histogram showing oxygen desaturation in groups A (■ = 0 cm H_2O CPAP), B (□ = 2.5 cm H_2O CPAP) and C (▨ = 5 cm H_2O CPAP).

Ventilatory frequency was similar in the groups, although the end-tidal concentrations of carbon dioxide increased significantly in patients who received CPAP (table IV). There was no significant difference between the two study groups for the percentage of time that CPAP, and hence a gas tight seal, was maintained (72% for group B, 64% for group C). Temporary loss of CPAP occurred, as anticipated, during insertion of the dental prop and pack and jaw manipulation.

The mean baseline heart rate in the three groups was similar. In all groups, the majority of patients displayed a mean increase in heart rate

TABLE V. *Mean (SEM) heart rate and arrhythmias, and number of ventricular ectopic beats in groups A, B and C.* n = *No. patients*

	Heart rate (beat min^{-1})			Ectopic beats
	Baseline	Increase	Decrease	(No. min^{-1})
Group A	89 (2.6)	41 (3.3)	22 (12.2)	1–2
	(n = 50)	(n = 46)	(n = 4)	(n = 6)
Group B	99 (2.6)	35 (2.5)	40 (12.2)	0.5–6
	(n = 48)	(n = 43)	(n = 5)	(n = 7)
Group C	101 (2.6)	33 (2.9)	39 (6.0)	0.5–3
	(n = 50)	(n = 44)	(n = 6)	(n = 6)

TABLE VI. *Incidence of hypoxaemia exceeding 10% of baseline* Sp_{O_2} *for different grades of anaesthetist and surgeon. SHO = Senior House Officer; SR = Senior Registrar; Reg. = Registrar; Cons. = Consultant*

	Anaesthetist (Total in each grade)			Surgeon (Total in each grade)		
	Student	SHO/Reg.	SR/Cons.	Student	SHO/Reg.	SR/Cons.
Group A	2 (20)	3 (11)	7 (19)	6 (24)	6 (25)	0 (1)
Group B	0 (4)	5 (39)	1 (7)	3 (23)	3 (27)	—
Group C	2 (6)	0 (25)	1 (19)	0 (19)	3 (29)	0 (2)
Total	4 (30)	8 (65)	9 (35)	9 (66)	12 (81)	0 (3)
(A+B+C)	13%	12%	25%	14%	15%	—

during operation. In a small number of patients there was a reduction in heart rate, but none required treatment. There was no significant difference between the three groups with regard to the incidence or duration of arrhythmias (table V).

Three-way analysis of variance between the groups and grades of anaesthetist and surgeon, showed no significant difference ($P = 0.89$) for the incidence of desaturation (table VI).

DISCUSSION

Hypoxaemia during dental extraction under nasal mask anaesthesia is often rapid in onset, not always obvious clinically [1, 13–15], and reported to be a major contributory factor to death from dental anaesthesia [16]. Pulse oximetry provides an advance in monitoring by detecting small reductions in oxygen saturation and displaying trends [10, 17].

Historically, low inspired oxygen concentrations were used for dental extraction under inhalation general anaesthesia. Increasing the fractional inspired oxygen concentration (FI_{O_2}) to 0.3 reduced the incidence and severity of peroperative desaturation compared with an FI_{O_2} of 0.2 or 0.25 [18], but it has been shown that a further increase in FI_{O_2} to 0.5 does not improve peroperative oxygen saturation [19]. This led to the investigation of the value of nasal CPAP on peroperative oxygen saturation in this study.

In young children, airway closure occurs at lung volumes well above FRC, producing a relatively high intrapulmonary shunt [20, 21]. During general anaesthesia, when there is further reduction in FRC, this intrapulmonary shunt is exacerbated [20–22] and, together with the propensity for upper airway obstruction caused by rhinitis and lymphoid hypertrophy in this age group, there is greater tendency to hypoxia.

Several studies have suggested two mechanisms whereby CPAP may enhance gas exchange and oxygenation in these children. First, there is an increase in FRC proportional to the CPAP [7, 8]. Second, CPAP may overcome apnoea and partial soft tissue airway obstruction [6]. In addition, the application of CPAP may rectify breathing in children with irregular breathing patterns [23]. In this study the application of 5 cm H_2O of CPAP resulted in a significant reduction in the incidence and severity of peroperative oxygen desaturation.

The increased ventilatory frequencies recorded during anaesthesia were consistent with similar studies in children receiving inhalation general anaesthesia with halothane [24].

The use of a pressure monitor in the circuit permitted attainment of the correct value of CPAP with a small fluctuation in pressure of ±1 cm H_2O noted throughout the ventilatory cycle. Reductions in pressure within the circuit alerted the anaesthetist to malposition of the pack, whereas a loss of pressure variations suggested airway obstruction or apnoea, and allowed early detection and repositioning of the jaw or mask before significant desaturation occurred. Pressure monitoring is also essential to guard against the potential hazard of inadvertent application of excessive CPAP [25].

One consideration in choosing the most appropriate breathing system for anaesthesia is its effect on the work of breathing. It has been shown that, when airway pressure is kept constant with increasing CPAP, the inspiratory work performed by the subject is decreased [26–29]. The 4-litre reservoir bag, wide bore tubing and high fresh gas flows ensured that marked fluctuations in airway pressure did not occur. The system described in this study for the application of CPAP would not, therefore, theoretically affect adversely the work of breathing, but may indeed reduce it.

Random allocation of patients in this study was impractical for several reasons, and the possibility of sequential error remains. Unlike a previous investigation [1], the grade of anaesthetist or surgeon was found to have no significant effect on peroperative oxygenation in either this or another study comparing an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.3 with an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.5 [19]. Surprisingly, the percentage incidence of hypoxaemic episodes for senior anaesthetists was twice that of junior trainees and dental students, while trainee and student dental surgeons seemed to contribute equally to these episodes (table VI). Although, on occasions, oxygen saturation decreased to as little as 80%, obvious cyanosis was not reported by the anaesthetists or detected by the observers in any patient. This may have resulted from the close monitoring used for the purposes of this study, and underlines further the value of such practice in routine anaesthesia.

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EFFECT OF VERAPAMIL ON RIGHT VENTRICULAR PRESSURE AND ATRIAL TACHYARRHYTHMIA AFTER THORACOTOMY

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SUMMARY

We have studied the effect of verapamil on the incidence of ECG changes and right ventricular pressures (RVP) in 25 male patients (aged 62 (SD 9) yr) undergoing thoracotomy in a placebo-controlled double-blind trial. Verapamil 0.01 mg kg^{-1} h^{-1} (n = 12) or saline (n = 13) i.v. was started after surgery and continued on the first day after operation with oral verapamil 80 mg or placebo, 8-hourly. Haemodynamic data were collected before operation and on three days after operation with the patients breathing air and then 60% oxygen ($F_{I_{O_2}}$ 0.60) for 10 min. Atrial tachyarrhythmia (AT) (4/13) and new ischaemic ECG changes (3/13) occurred only in the control group ($P < 0.05$). With an $F_{I_{O_2}}$ of 0.21, systolic RVP increased by 54% on the first two days after operation in the control group and by 13% in the verapamil group ($P < 0.02$). With an $F_{I_{O_2}}$ of 0.60 for 10 min, systolic RVP decreased more in the control than in the verapamil group ($P < 0.01$). In the control group, an increase in end-diastolic RVP ($P < 0.001$) and central venous pressure ($P < 0.05$) on the first day after operation was predictive of AT occurring on the second day.

KEY WORDS

Anaesthesia: thoracic. Complications: arrhythmia, postoperative. Heart: right ventricular pressure, verapamil

Hypoxaemia in chronic pulmonary disease elicits global hypoxic pulmonary vasoconstriction (HPV) which is responsible for cor pulmonale and right ventricular failure [1]. After lung resection, especially following pneumonectomy, the total blood volume perfusing the remaining lung is relatively increased. Thus the combination of increased blood volume and HPV stresses the right side of the heart and atrial fibrillation may occur after operation in about 20% of patients [2]. In this situation, dilatation of the pulmonary vascular bed may be helpful. Verapamil has been shown to inhibit HPV *in vitro* [3] and prevent right ventricular hypertrophy caused by HPV in rats with chronic hypoxaemia [4]. The sustained effect of verapamil (not possessed by other calcium channel blockers) may be related to its active hepatic metabolite, norverapamil, which has 50% of the potency of the parent compound [5]. Verapamil also has an effective antiarrhythmic action on the atrioventricular node [6].

In a double-blind, randomized placebo-controlled study, we have examined the effect of verapamil on right ventricular pressures, pulmonary gas exchange, systemic haemodynamics and cardiac rhythm in patients after thoracotomy.

PATIENTS AND METHODS

We studied 25 male patients undergoing elective thoracotomy (table I). The study was approved by the local Ethics Committee and informed consent was obtained from all patients. Patients receiving digitalis or beta-blockers or with an unstable cardiovascular state were excluded.

After arrival of the patient in the operating theatre, a cannula was inserted into a vein and

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TABLE I. *Preoperative characteristics and types of operation (mean values* (SD) *or number of patients)*

	Control ($n = 13$)	Verapamil ($n = 12$)
Age (yr)	64 (9)	60 (8)
Weight (kg)	72 (17)	76 (12)
Forced expiratory volume (% of predicted)	78 (17)	70 (10)
Diffusing capacity (% of predicted)	68 (21)	70 (10)
Pa_{O_2} (kPa)	11.1 (1.47)	11.2 (1.47)
Pa_{CO_2} (kPa)	5.2 (0.27)	5.3 (0.53)
Ischaemic heart disease suggested by		
History	3	4
ECG	3	6
Smoking more than 20 yr	10	11
Operations		
Explorative thoracotomy	4	2
Lobectomy	6	6
Bilobectomy	1	1
Pneumonectomy	2	3
Right thoracotomy	9	10
Left thoracotomy	4	2
Malignant tumour	10	9
Benign disease	3	3

fentanyl 0.1 mg given i.v. The radial artery on the side contralateral to the planned thoracotomy was cannulated. A balloon tip pulmonary catheter (Swan–Ganz, Monitoring Catheter, 7-French gauge, American Edwards Laboratories) with a sheath introducer set (Arrow, Inc., Reading, PA, U.S.A.) was inserted into the right ventricle. Right ventricular pressure (RVP) was measured in triplicate with the balloon inflated and a ventricular waveform present. Simultaneously, mean arterial pressure, heart rate, cardiac rhythm (electrocardiogram lead V5), central venous pressure (CVP) and arterial and mixed venous (right ventricle) blood-gas tensions were assessed. Intravascular pressures were measured electronically relative to atmosphere, using a zero level located at midthoracic height (Transpac II transducers, Abbott Laboratories). Arterial blood samples were obtained for immediate measurement of haemoglobin concentration, oxygen tension and oxygen saturation (Radiometer OSM2 oximeter).

Oxygen content was calculated as follows: (haemoglobin × 1.34 × percent saturation) + (oxygen tension (kPa) × 0.0004). Pulmonary shunt was calculated from the standard equation. Oxygen extraction index (EI_{O_2}) was calculated as $(Sa_{O_2} - Sv_{O_2})/Sa_{O_2}$ [7]. After preoperative measurements had been obtained, a standard anaesthetic technique was administered with thiopentone, fentanyl and enflurane and 50% nitrous oxide in oxygen. Vecuronium was used to provide neuromuscular block.

At the end of the operation, stratification was performed according to the extent of the operative procedure: explorative thoracotomy, lobectomy or pneumonectomy. Then the patients were allocated randomly to receive either verapamil 0.01 mg kg^{-1} h^{-1} (12 patients) or saline infusions (13 patients) in the recovery room. Verapamil 80 mg or placebo was given orally three times daily from the first morning after operation for 1 week. The patients breathed 60% oxygen (FI_{O_2} 0.60) after tracheal extubation until they were discharged from the recovery room. Oxygen therapy was continued with 35% oxygen by mask until the first morning after operation. Thereafter, all patients breathed room air (FI_{O_2} 0.21). Measurements were performed immediately after the patient arrived in the recovery room, 2 h after starting the infusions, on the first three mornings after operation, first with an FI_{O_2} of 0.21 and then with an FI_{O_2} of 0.60 for 10 min. Measurements were performed by the same investigator (L.L.) who was unaware of the randomization and medication. Between measurements, the tip of the pulmonary artery catheter was withdrawn into the superior vena cava.

An infusion of Ringer's acetate solution was given during operation at a rate of 1.5 ml kg^{-1} h^{-1}. No colloids were used. Haemoglobin concentration and PCV were maintained at acceptable values with transfusion of packed red cells combined with crystalloid solutions. All patients started with a light liquid oral diet on the first morning after operation. CVP was maintained at 5–10 mm Hg during the study.

In each patient, a 12-lead electrocardiogram (ECG) was obtained before operation and again after operation on the next three consecutive mornings. In addition to these routine ECG, serial ECG were recorded when necessary—for example when there were cardiac signs or symptoms or changes observed on the continuous oscilloscope monitoring. A chest x-ray was obtained daily and interpreted by an uninformed, experienced radiologist. Special attention was paid to development of venous congestion or atelectasis. If needed, bronchial lavage was performed, followed by minitracheotomy to remove secretions. Postoperative atelectasis was treated by tracheal intubation and hyperinflation. Measurements were always obtained before therapeutic procedures. Postoperative pain was treated with oxycodone 0.14 mg kg^{-1} i.m. on request or, if necessary, with intercostal blocks.

Plasma concentrations of verapamil and norverapamil

Arterial blood samples were obtained in heparinized tubes 2 h after the infusions had been completed and on the first and second mornings after operation for measurement of plasma concentrations of verapamil and norverapamil according to the method of Marvola and colleagues [7]. For the calculation of mean concentrations, values less than 25 ng ml^{-1} (lower limit of calibration) were considered as zero.

Statistics

Comparison of the effects of treatments was performed by multivariate analysis of variance for repeated measurements with treatment as the between-subjects factor and data points as the within-subjects factor. Roy's largest root [8] was used as the test criterion. If the effect of the interaction of data point and treatment was significant at a $P < 0.05$ level, multiple comparisons between the treatments were performed at different data points. In order to achieve a simultaneous significance level of $P < 0.05$ in each test, comparisonwise level of $P < 0.0083$ was chosen. The effect of haemodynamic variables on predicting the appearance of atrial tachyarrhythmia (AT) was assessed retrospectively using the same methods. Fisher's exact probability test with a correction factor [9] was used for ECG changes. $P < 0.05$ was considered significant. Results are expressed as mean (SD).

RESULTS

Pulmonary and cardiovascular status and surgical procedures were comparable in the two groups (table I). All patients had normal preoperative cardiac performance on exercise testing. Before operation, PCV, haemoglobin and plasma electrolyte concentrations and arterial pH were within normal limits in both groups. At 2 h and during the three-day postoperative follow-up, no significant changes occurred in these variables. Peroperative bleeding was 488 (SD 186), 400 (187) and 375 (263) ml in the verapamil and control groups and in the control patients with AT, respectively. The volume of Ringer's acetate infused i.v. was 26 (7) ml kg^{-1} in the verapamil group, 28 (8) ml kg^{-1} in the control group and 25 (3) ml kg^{-1} in the control patients with AT during the first 24 h. During the last 10 of the 24 h, 5% glucose 12 ml kg^{-1} was infused i.v. in all patients. On average, 0.8 units of packed red cells were given to each patient in the verapamil and control groups, and 0.7 units to those in the AT group. Because of excessive secretions, it was necessary to perform bronchial lavage, minitracheotomy, or both, in five of 12 verapamil and in four of 13 control patients on the first or second day after operation. Lobar atelectasis occurred in two patients in each group. Verapamil patients were discharged from the hospital after 9.7 (3) days and control subjects 10.7 (3) days.

ECG changes and cardiac rhythm

The groups were similar with respect to the extent of ischaemic heart disease as revealed by medical history and preoperative ECG findings (table I). All the patients had sinus rhythm before operation. On the second day after operation four of 13 control patients had a rapid supraventricular rhythm with a ventricular response of 142 (29) beats min^{-1}. Three patients had atrial fibrillation. The fourth patient had a supraventricular rhythm, probably junctional in origin, with a ventricular rate of 165 beat min^{-1}. No cardiac arrhythmias occurred in the patients treated with verapamil ($P < 0.05$). Verapamil 5 mg was administered i.v. to all patients with tachyarrhythmia, without a response. In two of the four patients with AT, administration of digitalis and quinidine restored sinus rhythm within 4 h and in the other two, cardioversion was necessary. In three of the control patients, transient ischaemic ECG changes occurred on the first or second day after operation, whereas in the patients receiving verapamil, no ischaemic changes were observed ($P < 0.05$) (table II).

Haemodynamics

Verapamil had no effect on circulatory variables. Heart rate remained at its initial value throughout the study, except in those control patients who had AT on the second day after operation. Mean arterial pressure was normal and similar in both groups. CVP was comparable in the study groups on the day of surgery. On the

TABLE II. *New ECG changes during the study (number of patients). The new ischaemic changes occurred on the first or second day after operation. Tachyarrhythmias always occurred on the second day. Significant differences, control vs verapamil:* *$P < 0.05$; **$P < 0.01$. *One patient with ischaemic ECG changes later developed atrial fibrillation*

Changes	Control ($n = 13$)	Verapamil ($n = 12$)
Atrial fibrillation	3*	0
Supraventricular tachycardia (junctional)	1*	0
Transient ischaemic ST–T changes	3*	0
Total	6**	0

first day after operation, the control patients who developed AT the next day had a significantly greater CVP than patients in the verapamil group and control patients without tachyarrhythmia ($P < 0.05$) (table III). Venous congestion was not seen in the chest x-ray in any patient during the three-day follow-up. Systolic RVP was normal and comparable before anaesthesia, before and 2 h after the start of verapamil or saline infusions in both groups. In the verapamil group, systolic RVP remained at approximately the baseline value and was decreased only slightly by administration of an $F_{I_{O_2}}$ of 0.60 on the first three days after operation. In the control group, systolic RVP was significantly increased on the first three days after operation with an $F_{I_{O_2}}$ of 0.21 ($P < 0.02$). Systolic RVP peaked on the second day after operation. An $F_{I_{O_2}}$ of 0.60 for 10 min decreased systolic RVP significantly on the first, second, and third ($P < 0.01$) days after operation (fig. 1). Exposure to an

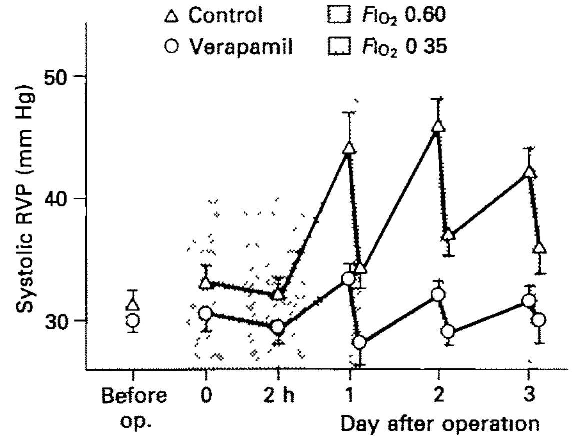

FIG. 1. Mean (SEM) systolic right ventricular pressure (RVP) before operation, immediately after operation (0), 2 h after the start of verapamil 0.01 mg kg^{-1} h^{-1} ($n = 12$) or saline infusions ($n = 13$) (2 h) and on the first three days after operation. Verapamil 80 mg, 8-hourly or placebo orally was started on the first day after operation. Patients breathed ambient room air except when indicated by stippling. Exposure to $F_{I_{O_2}}$ 0.60 on the postoperative days was for 10 min. Verapamil decreased RVP to values significantly less than control ($P < 0.05$). A significant difference ($P < 0.05$) between the groups, irrespective of $F_{I_{O_2}}$, was observed.

$F_{I_{O_2}}$ of 0.60 or verapamil did not decrease end-diastolic RVP significantly (fig. 2). However, when the end-diastolic RVP was analysed retrospectively for occurrence of AT, a significant difference ($P < 0.001$) was observed between patients with and without AT. In the control patients with AT on the second day after

TABLE III. *Haemodynamic variables in the treatment groups (mean values (SD)). AT = atrial tachyarrhythmia; HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure.* *$P < 0.05$ *compared with the other two groups*

	Before op.	After 2 h infusion	Day after operation 1	2	3
Control with AT ($n = 4$)					
HR (beat min^{-1})	77 (12)	86 (12)	85 (12)	141 (29)*	87 (12)
MAP (mm Hg)	86 (8)	90 (8)	84 (6)	88 (13)	83 (15)
CVP (mm Hg)	7 (2)	7 (3)	11 (2)*	9 (1)	7 (4)
Control without AT ($n = 9$)					
HR (beat min^{-1})	70 (9)	78 (13)	79 (6)	84 (8)	73 (10)
MAP (mm Hg)	89 (15)	85 (11)	98 (7)	101 (13)	92 (7)
CVP (mm Hg)	8 (2)	6 (3)	7 (3)	8 (3)	7 (2)
Verapamil ($n = 12$)					
HR (beat min^{-1})	78 (10)	86 (17)	81 (9)	88 (11)	83 (11)
MAP (mm Hg)	95 (12)	85 (10)	87 (9)	91 (12)	85 (6)
CVP (mm Hg)	8 (2)	8 (4)	7 (3)	7 (3)	9 (3)

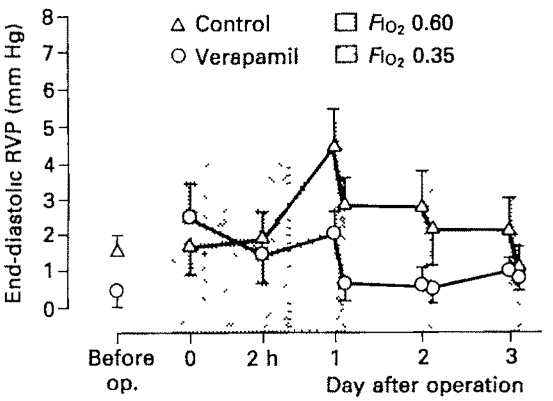

FIG. 2. End-diastolic right ventricular pressure (RVP) in the two study groups. For additional explanation, see figure 1.

operation, end-diastolic RVP increased five-fold from baseline on the first day (fig. 3). Clinically, no left ventricular abnormality was found in any of the patients. Arterial pressure was unaffected in all patients, and in those with AT.

Pulmonary gas exchange

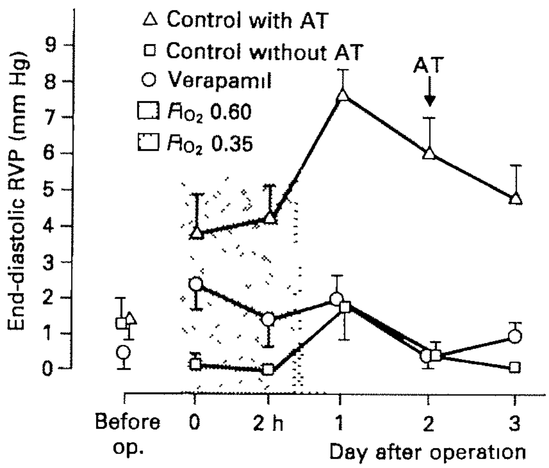

FIG. 3. End-diastolic right ventricular pressure (RVP) in the control patients with atrial tachyarrhythmia (AT) and in those without AT. There is a significant difference between control patients with AT and all other patients combined on the first day after operation ($P < 0\ 001$). ↓ indicates the day when AT occurred. For additional explanation, see figure 1

Arterial oxygen and carbon dioxide tensions and pulmonary shunt were similar at the time of the patients' admission to hospital (table I) and before and after operation (table IV). Arterial oxygen tension decreased and the pulmonary shunt increased significantly ($P < 0.05$) 2 h after

TABLE IV. *Pulmonary gas exchange in the treatment groups. AT = atrial tachyarrhythmia; VA = venous admixture;* EI_{O_2} *= oxygen extraction *P < 0 05 compared with preceding value*

	Before op.	After op.	After 2 h infusion	Day after operation				
				1		2		3
$F\text{I}_{O_2}$	0.21	0 60	0.60	0.21	0 60	0 21	0.60	0 21
Control with AT ($n = 4$)								
Pa_{O_2} (kPa)	10 1 (0.9)	30 (5 2)	32 3 (4.4)	7 6 (0.7)	27.5 (5.1)	8 (1.5)	26 (8)	8.3 (1.7)
Sa_{O_2} (%)	94 (2)	99 (1)	99 (1)	90 (2)	99 (1)	91 (5)	99 (1)	92 (3)
Sv_{O_2} (%)	76 (4)	81 (2)	84 (5)	64 (7)	77 (3)	64 (9)	76 (5)	65 (8)
VA (%)	24 (2)	6 (2)	6 (1)	28 (5)	5 (2)	25 (6)	5 (2)	26 (4)
EI_{O_2} (%)	20 (3)			30 (7)		30 (7)		26 (4)
Control without AT ($n = 9$)								
Pa_{O_2} (kPa)	11 1 (3.6)	29 (4 5)	27 (4.8)	9 1 (3.1)	28.9 (7.6)	9 1 (3.1)	27.1 (7.5)	9.1 (3.1)
Sa_{O_2} (%)	94 (4)	99 (2)	99 (0.5)	91 (4)	99 (1)	92 (5)	99 (1)	92 (2)
Sv_{O_2} (%)	72 (6)	78 (4)	79 (3)	68 (7)	77 (6)	68 (6)	78 (4)	67 (6)
VA (%)	22 (9)	7 (6)	5 (2)	28 (10)	5 (3)	25 (12)	6 (4)	24 (10)
EI_{O_2} (%)	24 (7)			25 (8)		26 (5)		23 (4)
Verapamil ($n = 12$)								
Pa_{O_2} (kPa)	10 (0 7)	28 (6.7)	24 9 (10.7)*	7 7 (1 9)	23 (9 3)	7 6 (1.6)	26 7 (9 5)	7.6 (1.5)
Sa_{O_2} (%)	95 (1)	99 (1)	98 (3)	87 (7)	99 (1)	88 (7)	99 (2)	88 (6)
Sv_{O_2} (%)	72 (1)	78 (5)	75 (5)	62 (8)	74 (4)	62 (6)	76 (3)	62 (5)
VA (%)	21 (5)	5 (4)	8 (8)*	30 (14)	7 (4)	30 (13)	7 (6)	30 (6)
EI_{O_2} (%)	24 (5)			31 (5)		30 (5)		31 (3)

the start of infusion of verapamil. These changes did not occur in the control group. On the three days after operation, arterial haemoglobin oxygen saturation was greater than 90% in the control group. Pulmonary shunt was somewhat higher in the verapamil than in the control group (ns) (table IV). Exposure to an $F_{I_{O_2}}$ of 0.60 for 10 min increased arterial oxygen tension and saturation significantly, and the pulmonary shunt decreased to the level of the anatomical shunt (table IV). Concomitantly, systolic RVP decreased (fig. 1). The changes in EIo_2 were similar to those in pulmonary shunt (table IV).

Plasma concentrations of verapamil and norverapamil

After 2 h of infusion, the mean plasma concentration of verapamil was 3 (11) ng ml^{-1}. On the first and second days after operation, the mean concentrations of verapamil were 44 (50) and 240 (116) ng ml^{-1}, respectively. Norverapamil was not detectable after 2 h of infusion of verapamil. On the first and second days after operation, the concentration of norverapamil was 15 (31) and 122 (56) ng ml^{-1}, respectively.

DISCUSSION

Thoracotomy-induced hypoxaemia caused an increase in systolic RVP, probably because of acute pulmonary vasoconstriction. The increase in both end-diastolic RVP and CVP in 30% of the control patients was associated with atrial tachyarrhythmia. These changes did not occur in the patients treated with verapamil.

Systolic RVP decreased more in the control patients exposed to 60% oxygen, than in the verapamil group. This suggests that the increase in RVP in our control group was caused by HPV and that, in the verapamil group, the HPV reflex was attenuated. After operation, the patients treated with verapamil had a smaller arterial oxygen tension and greater pulmonary shunt than the control patients receiving an $F_{I_{O_2}}$ of 0.21. The changes in oxygen extraction index parallelled the changes in pulmonary shunt and supports the view that oxygen extraction increased for pulmonary reasons [10] and may indicate that in the control group HPV was maintained and in the verapamil group it was inhibited, probably because of perfusion of non-ventilated alveoli [11]. Both diltiazem [12] and nifedipine [13] have been found to inhibit HPV, but in the case of nifedipine the effect seems to attenuate rapidly [14]. Although arterial oxygenation was impaired in the verapamil group, no new ischaemic ECG changes occurred, possibly because it has a coronary vasodilating effect [15] and diminishes work load in the ischaemic heart [16]. With oral therapy, as in the present study, verapamil does not affect left ventricular performance at rest [16].

In our study, an increase in end-diastolic RVP and CVP was associated with AT, mostly atrial fibrillation. Arrhythmia did not correlate with the extent of surgery. Tachyarrhythmia after thoracotomy occurs more often following pericardial dissection or if the patient develops interstitial pulmonary oedema [17]. These factors were absent in our patients, in whom the amount of fluid given during the first 24 h was less than suggested by Zeldin and others [18]. The absence of arrhythmia in our verapamil group may demonstrate protection of the right ventricle by pulmonary vasodilatation and by an antiarrhythmic action through slow calcium channel block at the atrioventricular level [6].

Several vasodilators, for example nitroglycerin, sodium nitroprusside and hydralazine, have been used in the therapy of pulmonary hypertension, but they all seem to cause systemic hypotension in humans [19]. In our study, there was acute right ventricular strain and treatment with verapamil, started immediately after the surgery, obviated this strain at the expense of slightly smaller arterial oxygen tensions and greater pulmonary shunt. In this respect, verapamil may possess a similar action as in left ventricular strain [16]. Verapamil has been shown to produce a prolonged beneficial effect in primary pulmonary hypertension [20, 21]. Verapamil has also been shown to be tolerated well in patients with obstructive pulmonary disease [22].

In our patients given verapamil, the plasma concentrations of the drug were in the therapeutic range in most patients on the first and in all patients on the second day after operation [23] when AT and ischaemic ECG changes occurred in the control group. The concentration of the active metabolite, norverapamil was also high, especially on the second day after operation. This may account for the efficacy of verapamil therapy in this study.

Post-thoracotomy cardiac tachyarrhythmia remains a troublesome clinical problem [24]. The results of our study show that prophylactic verapamil therapy in elderly smokers, particularly with concomitant coronary artery disease, undergoing thoracotomy may protect the right ventricle against HPV and prevent atrial tachyarrhythmia in the immediate postoperative period. Verapamil therapy can be indicated if the CVP or end-diastolic RVP increases on the first day after operation, as this may herald the onset of atrial tachyarrhythmia. The use of verapamil was associated with slightly increased pulmonary shunt and oxygen therapy, monitored by pulse oximetry, should be continued, therefore, for at least two days after operation.

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ELECTROENCEPHALOGRAPHIC CHANGES DURING VITAL CAPACITY BREATH INDUCTION WITH HALOTHANE

M. N. AVRAMOV, T. MURAYAMA, K. SHINGU AND K. MORI

SUMMARY

We investigated the EEG responses in 17 patients during induction of anaesthesia with vital capacity breaths of 4% halothane. The control alpha activity changed to a low voltage, 5–25 µV, fast, 20–28 Hz activity at the time of loss of consciousness at 78 (SD 27) s and typical spindle bursts (20–75 µV, 12–15 Hz) developed at 223 (51) s. All patients remained haemodynamically stable. This sequence of EEG changes was similar to that observed during induction with the conventional method of normal tidal volume breathing and a gradual increase of the inspired concentration of halothane.

KEY WORDS

Anaesthetic techniques: inhalation induction. Anaesthetics, volatile halothane Brain · electroencephalography

Although isoflurane is displacing halothane as a maintenance anaesthetic, halothane is less pungent and remains popular as an induction agent. The conventional method of induction with inhalation anaesthetics is normal tidal breathing with a gradual increase in concentration of the inspired anaesthetic. Rapid induction can be achieved either by administration of greater than clinical concentrations of the anaesthetic ("overpressure"), or by increasing the minute ventilation. The latter principle is the basis for induction with a single or several vital capacity (VC) breaths of 4% halothane [1–3] or 2% isoflurane [4]. These initial studies focused on evaluation of the safety, acceptance by patients, and clinical indications of this method.

EEG changes during induction of anaesthesia with the conventional method consist of an initial low voltage fast activity, followed by a gradual increase in amplitude and a gradual decrease in frequency [5]. During rapid induction with i.v. [6] and inhalation [7, 8] anaesthetics, a different sequence of EEG changes has been shown.

We therefore determined the effects of rapid induction with three VC breaths of 4% halothane on the EEG.

PATIENTS AND METHODS

The study was approved by the Institutional Human Investigation Committee. Seventeen patients (ASA grade I) undergoing elective gynaecological surgery gave informed consent for the study. Their average age was 37.9 (range 19–57) yr. All were free from neurological disorders and were not receiving any medication. No premedication was given.

A standard circle breathing system with a 3-litre anaesthetic bag attached to an anaesthesia machine with a calibrated halothane vaporizer (Fluotec Mark 3) was flushed for 5 min with 4% halothane in oxygen 10 litre min^{-1}; thereafter and during induction the flow was reduced to 8 litre min^{-1}. The expiratory valve was open at all times during induction, which followed the triple-breath technique [3]: after an exhalation to residual volume a VC breath of 4% halothane in oxygen was inhaled and, after a breath-hold of 20 s, was followed by a second VC breath held until 32 s, and a third VC breath held until 60 s. The volume of VC breaths was not measured directly, but only estimated. If unconsciousness was not attained within the first 60 s, the patient was requested to take additional breaths.

Before operation, the induction technique was explained in detail to the patients. Each patient

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was trained briefly in the technique. When a patient failed to hold her breath as long as required by the procedure, she was instructed immediately to exhale fully and take another VC breath. Consciousness was evaluated by the anaesthetist, blinded to the current EEG changes, at 10–15-s intervals. Unconsciousness was defined as the moment when the patient was unresponsive to a command to open her eyes and lost the eyelash reflex. After loss of consciousness, ventilation was assisted manually. Pancuronium 6 mg i.v. was given; the trachea intubated and the inspired halothane concentration reduced to 2%. The ECG was monitored continuously and systemic arterial pressure was measured non-invasively at 1–2 min intervals.

The EEG was recorded continuously, using a 10-channel EEG machine (San-Ei 1A91), from scalp disk electrodes filled with electroconductive paste and attached at frontal, parietal and occipital areas, with a reference at the earlobes.

RESULTS

Anaesthesia was induced successfully in 16 of the 17 patients. In one patient, following an incomplete first vital breath and because of extreme anxiety, the procedure was abandoned and an i.v. induction was used instead. The mean time for onset of unconsciousness was 77.9 (SD 26.9) s. There was much variability between patients in the timing of the second and the third breaths and in the duration of breath-holding. In general, all completed the third inspiration before 60 s. In nine patients the first three breaths were sufficient for induction; in three patients a fourth breath and in four patients a fifth breath was necessary. The duration of the first breath-hold of the latter four patients was also shorter, 10–15 s only, and the first breath was probably not to full VC. In all patients, the second, third and subsequent breaths were estimated to be less than VC as they were becoming partly anaesthetized.

The awake EEG of all patients was of alpha wave activity. The changes in EEG pattern during induction were similar for all. Initially, during performance of the respiratory manoeuvre, there was a decrease in amplitude and an increase in frequency. During the breath-holding intervals, EMG activity contaminated the EEG signal. At the time of loss of consciousness (77.9 (26.9) s), low amplitude (5–25 µV), fast (20–28 Hz) activity was recorded in all subjects (fig. 1). Thereafter, the general trend of EEG changes was of a gradual increase in amplitude and slowing in frequency, with the appearance of a spindle EEG pattern, typical of halothane, of 20–75 µV, 12–15 Hz activity at 223 (51) s (fig. 1). During the period from loss of consciousness to the spindle pattern, transitory bursts of theta waves appeared in seven patients. This theta activity was sometimes superimposed on the fast waves of the pattern of loss of consciousness and was not established as a

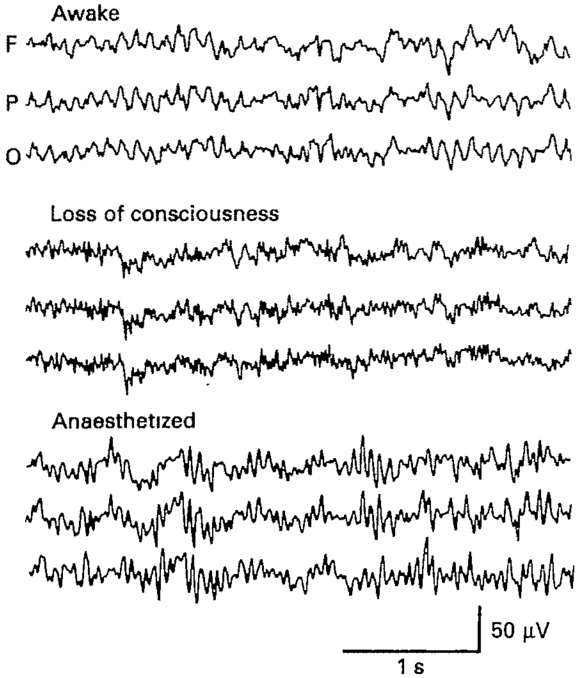

FIG. 1. Changes in the EEG during induction with three VC breaths of 4% halothane in a single patient. Monopolar recordings from left frontal (F), parietal (P) and occipital (O) areas with a reference electrode at the earlobe.

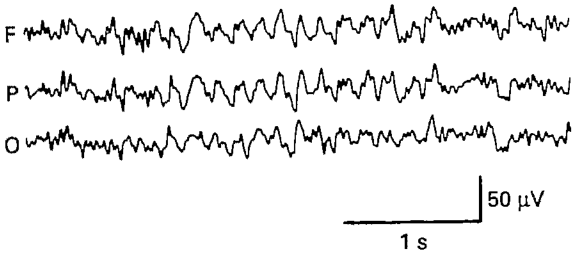

FIG. 2. A transitory theta wave burst at the stage of loss of consciousness. Such bursts of theta activity preceded the 12–15 Hz spindle EEG of halothane in seven patients. F = Frontal; P = parietal; O = occipital.

continuous pattern but was of short (10–20 s) duration only (fig. 2).

All patients remained haemodynamically stable with a moderate decrease in systemic arterial pressure (systolic 105 (10) mm Hg and diastolic 64.7 (5.8) mm Hg) immediately before tracheal intubation. The patients remained quiet and no excitation was observed.

DISCUSSION

Induction of anaesthesia with three vital capacity breaths of 4% halothane produced a gradual suppression of the control alpha EEG activity, a sign of wakefulness, and development of fast activity of 20–28 Hz, 5–25 μV, which coincided with loss of consciousness. There followed a progressive increase in amplitude and slowing in frequency and a typical spindle activity appeared. This sequence of changes of the EEG pattern in the present study was the same as that produced by conventional induction with halothane using normal volume ventilation and a gradual increase of the inspired concentration [5].

The difficulties of conducting satisfactory measurements in the circumstances of rapidly changing anaesthetic concentrations have been noted [9] and, in the present study, the end-tidal and arterial concentrations of halothane were not measured. Because the effect of hyperventilation is offset by the breath-holding, hypocapnia does not occur with this method of induction [3]. The rapid loss of consciousness in the present study may be attributed, therefore, to the rapid uptake of halothane by the brain and not to hypocapnia and decrease in cerebral blood flow.

Rapid induction of anaesthesia with a bolus of thiopentone [6, 10], 10% halothane [7] and 4% sevoflurane [8] has been associated with an unusual EEG response of suddenly appearing delta–theta range activity. With sevoflurane, this EEG pattern appeared during the initial rapid increase in the arterial concentration, and when it approached a plateau, a normal EEG pattern of 10–12 Hz spindle activity appeared [8]. The rate of increase in cerebral uptake of anaesthetics depends on the inspired concentration, the volume of ventilation and the blood solubility of the anaesthetic drug. Anaesthetics with lower blood/gas partition coefficients, for example sevoflurane (0.63, compared with halothane 2.3), have at the same inspiratory concentration a proportionately greater rate of increase in the anaesthetic partial pressure in arterial blood and brain. Halothane is 3.7 times more soluble than sevoflurane, and at 4% inspired concentration, sevoflurane produced the rapid induction type of EEG seen in our previous study [8] while, in the present study, halothane did not, even though the VC breath technique was used. The appearance of transitory theta activity in seven of the patients suggests that speed of induction with the present method approaches the rapid type induction with regard to the EEG criteria.

Studies from our laboratory and others have indicated that the delta–theta wave EEG is produced not only during extremely rapid induction of anaesthesia but also when some CNS stimulation is given to the anaesthetized [11–13] or the sleeping brain [14]. The neurophysiological significance of this EEG pattern is still not clarified in relation to the rapid induction of anaesthesia. The absence of unusual EEG changes in the present study provides additional support to the view that the induction of anaesthesia by vital capacity breathing is a safe and acceptable technique.

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ATTENUATION OF THE PRESSOR RESPONSE TO TRACHEAL INTUBATION IN HYPERTENSIVE PROTEINURIC PREGNANT PATIENTS BY LIGNOCAINE, ALFENTANIL AND MAGNESIUM SULPHATE

R. W. ALLEN, M. F. M. JAMES AND P. C. UYS

SUMMARY

The pressor response to intubation is known to be exaggerated in patients with gestational proteinuric hypertension (GPH). The effect of pretreatment with lignocaine 1.5 mg kg^{-1}, magnesium sulphate 40 mg kg^{-1} or alfentanil 10 μg kg^{-1} on this pressor response was studied in 69 patients with moderate to severe GPH. Systolic arterial pressure exceeded baseline values for the first 5 min after tracheal intubation in the lignocaine group, with a peak increase of 31.6 (SEM 3.6) mm Hg at 2 min after intubation, but no mean increase in pressure occurred in the two other groups. Following intubation, six of 24 mothers in the alfentanil group, six of 21 in the lignocaine group and one of 24 in the magnesium group ($P < 0.05$) exhibited a systolic arterial pressure (SAP) greater than 180 mm Hg sustained for 2 min or more. Alfentanil caused the least change in heart rate, but resulted in significant fetal depression.

KEY WORDS

Anaesthesia: obstetric Complications. gestational hypertension Intubation, tracheal alfentanil, pressor response, lignocaine, magnesium sulphate.

The pressor response to tracheal intubation is particularly marked in the hypertensive pregnant patient, with increases in systemic and pulmonary arterial pressures and pulmonary capillary wedge pressure [1, 2]. These changes have been associated with increased intracranial pressure, cerebral haemorrhage and cardiac failure with pulmonary oedema, resulting in increased morbidity and mortality in both mother and child [3]. Several techniques have been used to attenuate these haemodynamic responses, including topical and i.v. local anaesthetics, vasodilators, low and high doses of opioids and adrenoceptor blockers. The relevance of these methods to gestational proteinuric hypertension (GPH) has been reviewed recently [4], but none appears to be entirely satisfactory. Although lignocaine is advocated widely, and was our standard agent for attenuation of the pressor response before this study, its effectiveness, particularly in the more severe cases, has been questioned [2] and it may be harmful to the fetus [5]; with the opioids there is the risk of fetal depression, the vasodilators may produce serious hypotension, and the β-blockers may produce fetal hypoglycaemia. Of the opioids, alfentanil seems to be the most promising, with a very rapid onset and short duration of action [6]. At a dose of 10 μg kg^{-1}, in normal pregnancies, it was found to obtund the pressor response and produce minimal fetal depression [7]. It has not been tested extensively in patients with GPH, and caution is advocated with respect to possible detrimental effects on the fetus [8] and the mother [9].

Magnesium sulphate ($MgSO_4$) has been shown to inhibit catecholamine release [10] and to control both catecholamine release and the pressor response to tracheal intubation [11]. Its role in GPH has been established over many years [12]. It might therefore be considered to be a potentially valuable agent for use in GPH patients, but apart from one encouraging preliminary study [13], it

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has not been investigated in this context. We decided, therefore, to compare the effects of lignocaine, alfentanil and magnesium sulphate on stress responses to tracheal intubation in patients with moderate to severe GPH requiring Caesarean section under general anaesthesia.

PATIENTS AND METHODS

The study was approved by the human Ethics Committee of the University of Cape Town, and written informed consent was obtained from all participants.

Patients included in the study were pregnant hypertensives (diastolic arterial pressure > 90 mm Hg on two or more occasions) with proteinuria (2+ or more, using a multistix estimation) who required general anaesthesia for either elective or emergency Caesarean section. Patients in whom severe fetal distress was felt to preclude the post-induction delay needed for the study were excluded, as were patients whose disease was so severe that randomization of treatment was not considered acceptable. An increased serum concentration of creatinine was also a contraindication, as renal dysfunction may lead to difficulties in the elimination of magnesium.

Patients were allocated at random to one of three groups: group 1 received lignocaine 1.5 mg kg^{-1}, group 2 received $MgSO_4$ 40 mg kg^{-1}, and group 3 received alfentanil 10 μg kg^{-1}.

Patients meeting the above criteria for the diagnosis of GPH were managed initially by the obstetric staff, and no restraint was placed on the obstetric use of antihypertensive medication, but the drugs used and the time of the last dose were recorded. Antacid therapy with ranitidine 150 mg for elective cases, or oral sodium citrate 30 ml for emergencies, was given before surgery. On arrival in the operating theatre, patients were placed on the operating table with a right lateral tilt. Monitoring included routine ECG, capnography and pulse oximetry. Arterial pressure was recorded in one arm using an automated oscillotonometric device with printer (Dinamap, Critikon) with recordings at 1-min intervals. For the first 5 min after induction, the Dinamap was placed in the STAT mode which gave three or four readings per minute. Thereafter, readings were made at 1-min intervals. On the other arm, arterial pressure was recorded continuously, using a non-invasive finger cuff pressure recording system (Finapres, Ohmeda) connected to a pen recorder. This dual system was used as it allowed the detection of arterial pressure changes that might be too rapid for the Dinamap to follow, while it was felt that the accuracy of the Finapres was not yet sufficiently established [14]. Written records of both graphical representation of arterial pressure changes and numerical values of arterial pressure and heart rate were thus obtained. Where the Finapres indicated that an arterial pressure peak had occurred between Dinamap recordings, the highest value of pressure occurring during any 1-min interval was always used. Where there was disagreement between the monitors, the Dinamap was taken to be accurate, and the Finapres reading adjusted accordingly.

All patients received metoclopramide 10 mg i.v. and their lungs were then preoxygenated for 5 min using a circle system with a close-fitting face mask and oxygen 8 litre min^{-1}. At the end of this time, baseline cardiovascular measurements were made. Anaesthesia was induced with thiopentone 5 mg kg^{-1} over 10 s, followed by the study drug diluted to 10 ml in water also given over 10 s, and then suxamethonium 1 mg kg^{-1} i.v. Cricoid pressure was applied and tracheal intubation was performed 60 s after administration of the suxamethonium. Intubation was performed by an anaesthetist blinded to the study drug given. The time taken for laryngoscopy and intubation was noted. Anaesthesia was maintained for 10 min before the start of surgery with 50% nitrous oxide and 0.5% halothane in oxygen with ventilation adjusted to ensure normocapnia; during this time arterial pressure was measured continuously as described above. Muscle relaxation was maintained with an infusion of suxamethonium 4–8 mg min^{-1}, and neuromuscular function monitored using a nerve stimulator. Maternal blood was obtained for measurement of serum magnesium concentrations before induction, 1 min after intubation, at delivery and 30 min after induction.

At the end of the 10-min monitoring period, during which time the patient had been cleaned and draped, surgery commenced and the times from skin incision to delivery and uterine incision to delivery were noted. Cardiovascular responses to surgery (and later to extubation, although not part of the study) were noted. At delivery of the infant, cord blood was sampled for serum concentrations of magnesium and fetal acid–base status. Following delivery, neonates were scored on the Apgar system at 1 and 5 min by a paediatrician who was blinded to the study drug given. The

TABLE I. *Maternal characteristics (mean (SEM)). Emerg., Elect. = Numbers in each group undergoing emergency or elective procedures. *Significant difference between groups 1 and 2* (P < 0.05)

	Age (yr)	Weight (kg)	Gestational age (weeks)	Emerg.	Elect	Admission AP (mm Hg) Systolic	Diastolic	Mean
Group 1 ($n = 21$)	26.9 (1.4)	78.43 (3.6)	33.7 (0.8)	12	9	173.6 (4.9)	114.3 (2.2)	133.7 (2.2)
Group 2 ($n = 24$)	26.5 (1.0)	76.7 (14.8)	32.5 (0.7)	16	8	186.7* (3.8)	120.2 (2.1)	142.9 (2.7)
Group 3 ($n = 24$)	27.5 (1.1)	79.2 (3.4)	32.1 (0.7)	15	9	178.7 (4.3)	115.6 (1.7)	140.9 (4.7)

TABLE II *Premedication used in the 12 h before surgery to control the symptomatology of GPH in the three groups, and subsequent ward pressures (mean (SEM)). No significant differences between groups*

	Premedication						Ward AP (mm Hg)		
	Nil	$MgSO_4$	Methyldopa	Nifedipine	β-Blocker	Hydralazine	Systolic	Diastolic	Mean
Group 1 ($n = 21$)	4	14	3	6	1	2	149.1 (1.8)	100.2 (1.6)	121.5 (2.4)
Group 2 ($n = 24$)	2	13	8	9	2	2	154.6 (1.9)	101.9 (1.5)	116.8 (1.3)
Group 3 ($n = 24$)	4	12	4	6	1	2	152.7 (2.8)	101.3 (1.4)	118.5 (1.7)

paediatrician also recorded what resuscitative measures had been necessary, including the use of naloxone, and the response to this drug. More sophisticated neonatal behaviourial tests such as neonatal adaptive capacity scoring (NACS) were considered, but discarded, as almost all the infants were premature, and the NACS and similar systems are not appropriate in infants of less than 37 weeks gestation [15].

Statistical analysis was performed using analysis of variance, Student's *t* test with the Bonferroni modification for multiple comparisons, Wilcoxon rank sum and Fisher's exact tests where appropriate. The null hypothesis was rejected at $P < 0.05$.

RESULTS

There were 24 subjects in each of the alfentanil and magnesium groups, and 21 subjects in the lignocaine group. Subjects were well matched for maternal age and weight, gestational age and cardiovascular variables (table I), and there were no significant differences in routine biochemical variables between the groups. Two patients were excluded on the basis of fulminating disease of such severity that a diagnosis of phaeochromocytoma was considered. In these two patients, mean arterial pressures in excess of 220 mm Hg were recorded before induction of anaesthesia. Both were managed successfully with infusions of $MgSO_4$ 60 mg kg^{-1} and alfentanil 30 μg kg^{-1}, followed by our standard anaesthetic technique. These two patients were found not to have a phaeochromocytoma on subsequent investigation.

All but five of the subjects were diagnosed as having severe GPH on the basis of an initial diastolic arterial pressure of 110 mm Hg or greater. Of these patients, one was in group 2, with two in each of the other two groups. When arterial pressure had been stabilized in the obstetric high-care unit, cardiovascular data within the three groups were not significantly different (table II), and these values were taken as the baseline for subsequent comparisons. The overall mean systolic arterial pressure in all the subjects on admission was 179.9 (SEM 2.4) mm Hg. The use of antihypertensive medication within 12 h of surgery was basically similar in the three groups, and no patient received antihypertensive medication within 2 h of arrival in theatre.

Indicators of severity of the GPH, including the degree of proteinuria, the degree of oedema and the incidence of neurological, renal or hepatic events, were not significantly different between groups. Only one patient had suffered a con-

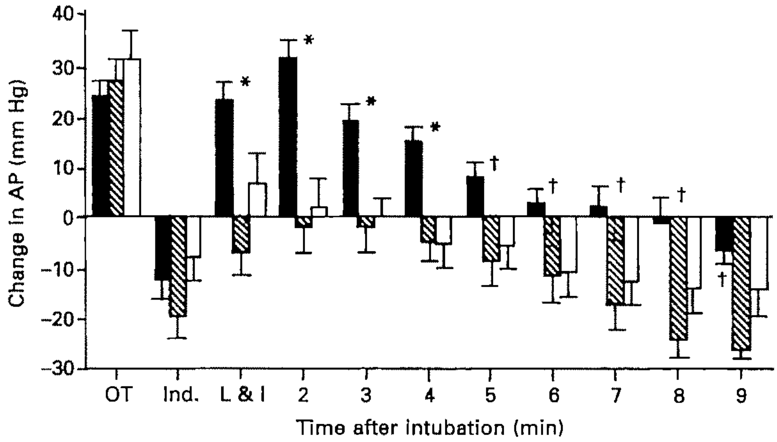

FIG. 1. Changes in systolic arterial pressure (AP) from ward baseline in the three groups (■ = lignocaine; ▧ = magnesium; □ = alfentanil). OT = Stable value with the patient settled on the operating table; Ind. = after induction of anaesthesia and administration of study drug; L&I = peak values following laryngoscopy and intubation *Group 1 (lignocaine) significantly different from groups 2 and 3 ($P < 0.01$); †group 1 significantly different from group 2 ($P < 0.05$).

vulsion before admission to the trial; she was in the magnesium group. There were no convulsions in any of the patients following admission to the obstetric unit. Of the 39 patients in the three groups who had received $MgSO_4$ before entry into the trial, eight still had serum concentrations of magnesium within the normal range, and only three had values generally regarded as therapeutic (> 2 mmol $litre^{-1}$). The mean serum concentration of magnesium attained in group 2 mothers immediately after tracheal intubation was 3.48 (0.32) mmol $litre^{-1}$. In the subgroup of these mothers who had received $MgSO_4$ before surgery, the mean serum concentration of magnesium attained was 4.01 (0.28) mmol $litre^{-1}$, and the greatest concentration attained in this group was 6.6 mmol $litre^{-1}$. At the time of delivery, the mean serum concentration of magnesium had decreased to 2.2 (0.12) mmol $litre^{-1}$ and at 30 min serum magnesium had decreased further to a mean of 1.75 (0.10) mmol $litre^{-1}$. No difficulties were experienced in re-establishing neuromuscular function at the end of the procedure.

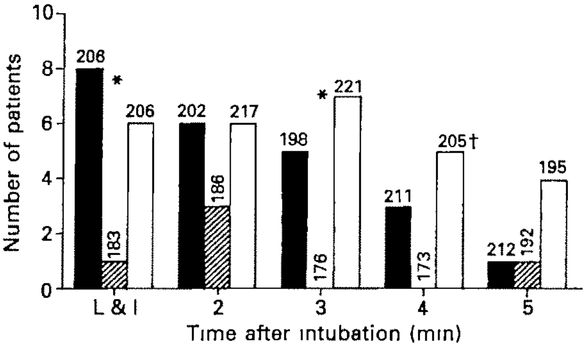

FIG. 2. Numbers of patients in each group (■ = lignocaine; ▨ = magnesium; □ = alfentanil) in whom systolic arterial pressure increased to more than 180 mm Hg after intubation. The peak pressure attained in each group at each point is shown above each column. *Groups 1 and 3 significantly different from group 2 ($P < 0.05$); †group 3 significantly different from group 2 ($P < 0.05$).

There was an increase in arterial pressure from ward values in all groups on arrival in the operating theatre, and induction of anaesthesia produced a similar reduction in arterial pressure in all groups. The mean increase in systolic, diastolic and mean arterial pressure following intubation was significantly greater in group 1 than that in the other two groups ($P < 0.01$) and remained significantly greater than that in group 2 for the entire study period (fig. 1). Patients were grouped also into those showing post-intubation SAP readings greater than the initial admission mean SAP (180 mm Hg). There were significantly more mothers with systolic arterial pressures greater than this in both group 1 and group 3 for the first 4 min after intubation than in group 2, and in this regard, groups 1 and 3 were indistinguishable (fig. 2), although it should be noted that in all but one patient in group 3 this represented a failure to reduce an arterial pressure increased during induction, rather than a failure

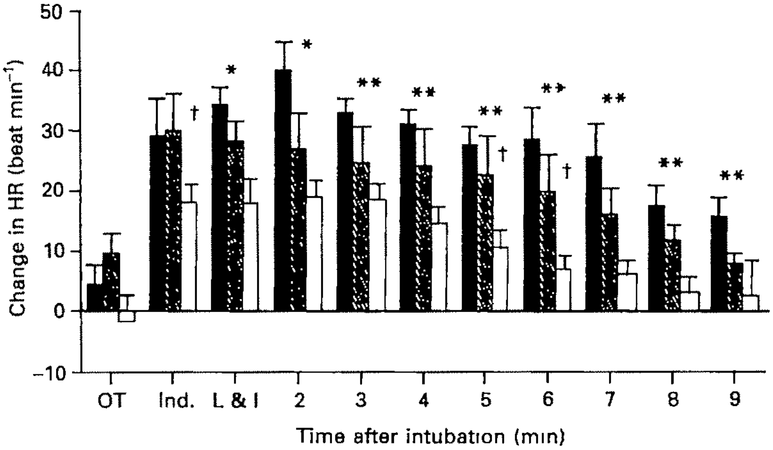

FIG. 3. Changes in heart rate (HR) from ward baseline in the three groups (■ = lignocaine, ▨ = magnesium; □ = alfentanil). OT = Stable value with the patient settled on the operating table; Ind. = after induction of anaesthesia and administration of study drug; L&I = peak values following laryngoscopy and intubation. *Group 1 significantly different from the other two groups ($P < 0.05$); **group 1 significantly different from group 3 ($P < 0.01$); †group 2 significantly different from group 3 ($P < 0.05$).

TABLE III. *Delivery and neonatal data. Numbers in parentheses = 1* SEM. *Apgar scores are medians. I–D, U–D = times from skin incision and uterine incision, respectively, to delivery; SV = number of infants initiating spontaneous ventilation without assistance; Naloxone Given = number of neonates receiving naloxone; Naloxone Effect = number of neonates responding with increased ventilation to naloxone. *Significantly different from the two other groups,* ($P < 0.05$); *†significantly different from group 2* ($P < 0.05$)

	I–D (min)	U–D (min)	Birth wt (g)	Fetal pH	Apgar score 1 min	Apgar score 5 min	SV	Naloxone Given	Naloxone Effect
Group 1 (*n* = 21)	4.7 (0.3)	1.0 (0.1)	1913.6 (163.1)	7.24 (0.01)	7	8	6	5	0
Group 2 (*n* = 24)	4.8 (0.5)	1.8 (0.3)	1771.7 (149.9)	7.23 (0.01)	7	8	13	1	0
Group 3 (*n* = 24)	4.7 (0.4)	1.2 (0.1)	1726.2 (177.6)	7.22 (0.92)	4*	7	3†	17†	9*

to prevent hypertension on intubation. This was not the case in group 1, in which most patients showed an increase in pressure from pre-induction values. Several patients showed greater variation in arterial pressure than that revealed in the Dinamap readings, particularly at the time of induction and intubation. Where this occurred, the peak or trough values obtained from the Finapres were taken, after confirmation of the accuracy of the Finapres readings from comparison with the appropriate Dinamap readings. In this study, correlation between the Finapres and the Dinamap readings was only fair ($r = 0.8$), with the Finapres tending to underestimate the pressure. In the subgroup of group 3 mothers who had received $MgSO_4$ before operation, there was a tendency towards smaller arterial pressures when compared with the remainder of this group, but this did not reach statistical significance.

Following intubation, heart rate did not increase in group 3 mothers, whilst heart rate decreased from post-induction values in group 2 mothers (fig. 3). Heart rate was significantly greater in group 1 than in the other two groups for the first 2 min after intubation. Rate–pressure products were very high in all groups, and group 1 was significantly worse than group 2 for the first 4 min after intubation, and than group 3 at all post-intubation data points ($P < 0.05$). Arrhythmias occurred in three patients in group 3, but were not observed in the other two groups. There were no difficult intubations, and the laryngoscopy and intubation time was less than 20 s in every patient, with no differences between groups.

All three groups showed significant increases in arterial pressure with the onset of surgery; the greatest increase was in group 1 (28.2 (5.1) mm Hg increase in MAP), and the least in group 3 (23.2 (4.7) mm Hg increase in MAP), but the between-group differences were not statistically significant, and despite this surge the arterial pressure did not exceed ward baseline at this time. At the end of the procedure, arterial pressure in all three groups was less than the ward baseline, and on extubation there was a significant increase in all three groups, similar in magnitude to the change with surgery, to values slightly above baseline.

Neonatal data are summarized in table III. The mean serum concentration of magnesium in group 2 infants was 1.35 (0.44) mmol $litre^{-1}$. There were three neonatal deaths in the study, one in each group, all of which were associated with very low birth weights (< 800 g in each case).

DISCUSSION

Alfentanil and magnesium were significantly better than lignocaine in containing the mean cardiovascular responses to intubation, and magnesium appeared to have less detrimental effect on the fetus. These results may have been slightly prejudicial to lignocaine, in that the optimum time of 2 min for the action of lignocaine was not allowed in the experimental design, although similar inadequate control using this agent has been reported by Connell, Dalgleish and Downing [2]. The time to maximum effect of $MgSO_4$ is not known, but previous studies have suggested that the agent should be effective within the time of this study [11]. Alfentanil reaches its peak activity between 60 and 120 s [16], and therefore the study design tended to favour this agent. This study design was chosen as it was felt that an ideal agent should be effective when given at the time of induction so that side effects of respiratory or reflex depression, or interference with muscle tone would not put the mother at added risk. The unpleasant sensation of heat produced by injection of $MgSO_4$ also implies that it would be preferable that the agent could be given at induction and still be effective. There was a failure to control SAP to 180 mm Hg or less for 4 min after intubation in 25% of mothers in the alfentanil group, despite the satisfactory overall mean values. As the objective is to prevent or control potentially injurious hypertension, this must be regarded as a relative failure of alfentanil pretreatment, which was little better than lignocaine in this regard. However, none of the agents was ideal, as at the 2-min post-induction point, several mothers in all the groups had SAP greater than the admission mean.

Although magnesium is not used widely in Europe, it is the standard agent used to prevent convulsions in patients with GPH in the U.S.A. [12] and is the agent of choice in our own obstetric practice. In addition to its anticonvulsant action, it produces widespread vasodilatation of most vascular beds, including uterine blood vessels [17], but it does not normally produce significant hypotension [18]. Consequently, it has been claimed to improve uterine blood flow, and to have a beneficial effect on the unborn child [19].

The mechanism of action of magnesium in limiting the pressor response to intubation is probably multifactorial. It has been demonstrated that magnesium inhibits the release of catecholamines *in vivo* at the time of intubation [11]. In addition, magnesium is an α-adrenergic antagonist and has direct vasodilator properties [20]. Despite this vasodilatation, magnesium does not generally produce significant hypotension because of a concomitant increase in cardiac output [21], but where this increase does not occur, marked hypotension may result. In the dose of $MgSO_4$ 40 mg kg^{-1} used in this study, no serious hypotension was encountered. This dose was chosen to allow blind administration of $MgSO_4$, regardless of pretreatment. In patients who have not received $MgSO_4$ before surgery, the more normal obstetric loading dose of 60 mg kg^{-1} might produce even better control in those patients in whom significant hypertension persisted after intubation. On the other hand, alfentanil appears to act primarily by inhibiting release of catecholamines by central depression [22]. Doses greater than those used in this study produce unacceptable hypotension [22], but the dose of 10 $\mu g\ kg^{-1}$ appears to produce satisfactory cardiovascular control without marked reductions in arterial pressure. Although magnesium produced greater reductions in arterial pressure than alfentanil, these differences were neither statistically nor clinically significant. The mean arterial pressure remained greater than 90 mm Hg at all times in both groups, and on no occasion did hypotension necessitating treatment occur. It should be noted that the decrease in arterial pressure which occurred in both groups 2 and 3 was partially a result of the delay required by the study design. Where the more normal practice of commencing surgery shortly after induction of anaesthesia is followed, these changes would probably not be seen. In this group of patients, the moderate tachycardia produced by magnesium is probably of no significance, and might even be of benefit in maintaining or increasing cardiac output.

Although it has been suggested that magnesium may have a deleterious effect on the neonate, a large study of infants born to toxaemic mothers who had received magnesium has failed to show any relationship between serum concentration of magnesium and neurobehavioural scores [23]. In the present study, no adverse effects of magnesium on the neonate were seen and no relationship between neonatal magnesium concentrations and neonatal Apgar scores, muscle tone, the establishment of spontaneous ventilation or acid–base state could be demonstrated. In contrast, alfentanil also crosses the placenta readily and severe fetal depression has been recorded following its use [8]. Protein binding of alfentanil in the neonate has been shown to be less than that in the adult, particularly in the preterm infant [8]. Marked (although readily treatable) respiratory depression was seen in neonates in group 3 of the present study. These results are at variance with those of Dann, Hutchinson and Cartwright [7], who found no fetal depression after the same dose of alfentanil as that used in the present study. However, their study examined healthy, full-term infants. The recommendation by Redfern and colleagues [8] that the use of alfentanil be limited to units in which good neonatal resuscitation and ventilation facilities exist would appear to be supported by the present study.

Magnesium has well known inhibitory actions at the motor end plate; at varying serum concentrations usually exceeding 5 mmol litre^{-1}, neuromuscular weakness occurs, followed by respiratory paralysis [23]. The widespread belief that magnesium potentiates the action of suxamethonium has not been supported by two recent human studies which were unable to show prolongation of the action of suxamethonium [24, 25]. Neuromuscular function was not studied specifically in this investigation, but no difficulty was experienced in recovery of our patients from a continuous infusion of suxamethonium.

In conclusion, magnesium and alfentanil have been shown to provide adequate control of the cardiovascular response to intubation in hypertensive pregnant patients, although alfentanil may be less reliable in controlling severe hypertension in some subjects. On the basis of this and previous studies, we suggest that it is difficult to justify the continued use of lignocaine in this area. Alfentanil produced better control of heart rate, but at the expense of fetal respiratory depression. As the two drugs act through entirely different mechanisms, the possibility that a combination of magnesium and alfentanil in lower doses may produce the benefits of both, with fewer side effects, is worthy of further investigation.

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COMPARATIVE STUDY OF THE EFFECTS OF AIR OR SALINE TO IDENTIFY THE EXTRADURAL SPACE

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SUMMARY

Fifty women in labour were allocated randomly to receive either air or saline to assist in the identification of the extradural space by the loss of resistance technique. A study volume of 4 ml of air or saline was used before 0.5% bupivacaine 8 ml and the spread of analgesia was followed for 30 min. The first segment blocked, time of onset, number of blocked segments and height of block were comparable in the two groups. At 30 min, there were eight patients with an unblocked segment in the air group, compared with two in the saline group ($P < 0.01$). All unblocked segments were blocked subsequently by further doses of bupivacaine. We conclude that air is more likely than saline to produce unblocked segments in the initiation of extradural analgesia in labour.

KEY WORDS

Anaesthesia obstetric. Anaesthetic techniques· extradural. Complications unblocked segments.

Since extradural analgesia was popularized by Dogliotti in the 1930s, a variety of techniques have been used to identify the extradural space. Today, the loss of resistance technique using either an air- or saline-filled syringe is the most popular method. The proponents of these two methods disagree about the relative advantages and disadvantages of each medium. However, there have been no prospective comparative studies on the possible effects of the injected air or saline on the subsequent analgesia.

The aim of this study was to determine if the choice of either air or saline in the loss of resistance technique would affect the onset, spread or character of the initial extradural injection of local anaesthetic in the patient in labour.

PATIENTS AND METHODS

Fifty primiparous patients in early labour who had requested extradural analgesia gave informed verbal consent to the study, which was approved by the local Ethics Committee. Patients who had previously experienced an extradural or spinal procedure, patients in whom urgent delivery was anticipated and those who had a contraindication to extradural analgesia were excluded from the study. The patients were allocated randomly to one of two groups to receive either air or 0.9% sodium chloride (saline) in equivalent volumes (4 ml) as part of the loss of resistance method of locating the extradural space. The blocks were undertaken by a group of five anaesthetists, including the investigators, all of whom had more than 3 years experience of extradural technique.

Under aseptic conditions and following local infiltration with 1% lignocaine 2–4 ml, extradural puncture was performed with a 16-gauge Tuohy needle (Portex) at either the L2–3 or the L3–4 interspace, with the patient lying in the left lateral position. Following puncture of the ligamentum flavum and satisfactory loss of resistance, 4 ml of the study medium was injected slowly into the space. A catheter was threaded through the Tuohy needle, leaving 2–4 cm in the extradural space. Before the extradural filter was attached, it was flushed with 0.5% bupivacaine in order to avoid (apart from the small deadspace of the catheter) injection of air on subsequent dosing.

As soon as the extradural catheter had been secured, a test dose of 0.5% bupivacaine 4 ml was

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given (time $t = 0$) and, in the absence of any complications, a further 4 ml was given after 5 min ($t+5$). All patients remained in the left lateral position for the 30-min duration of the study. An investigator who had no knowledge of the medium used to identify the extradural space assessed onset of sensory loss and dermatomal spread, using sterile 21-gauge needles to test pinprick at 5-min intervals up to 30 min ($t+30$). At this time, patients were asked if they felt any discomfort and unblocked dermatomal segments were noted. An unblocked segment was defined as one remaining sensitive to pinprick whilst adjacent segments above and below were pain free. Maternal heart rate and arterial pressure were recorded at 5-min intervals throughout the study.

After the 30-min study period, routine management was resumed. In patients with unblocked segments, measures were taken to ensure adequate extradural analgesia (*vide infra*).

Data on the onset and extent of sensory block between and within the two groups were analysed for statistical significance using Student's t test. The incidence of unblocked segments was assessed using chi-square tables with Yates' correction. Data on height of the block between groups were compared using the Wilcoxon rank sum test. $P < 0.05$ was taken as statistically significant.

RESULTS

Twenty-five patients received an injection of air and 25 saline, in the loss of resistance technique. There was no difference between the two groups in age, weight and height (table I).

There were no untoward cardiovascular side effects in either group, and no dural taps or other complications of extradural insertion.

There were a total of eight unblocked dermatomal segments in eight patients in the air group and two unblocked segments in two patients in the saline group ($P < 0.01$) (table II). All unblocked segments occupied either the T12 or L1 dermatome. Three unblocked segments occurred on the patient's left (dependent) side and seven unblocked segments on the right (uppermost) side.

Two patients in the air group had blocks which did not extend above L1 on one side (one right, one left). All unblocked segments were relieved after the 30-min study period by the injection of 0.5% bupivacaine 4 ml with the patient lying on the unblocked side.

TABLE I. *Patient characteristics (mean (SD or range))*

	Air group	Saline group
Age (yr)	25.3 (17–35)	24.7 (17–37)
Weight (kg)	75.2 (3.9)	73.8 (5.1)
Height (m)	1.67 (0.29)	1.65 (0.25)

TABLE II. *Number of patients with unblocked segments at time t+30 min. *P <0.01 between groups*

	Air group	Saline group
Right	6	1
Left	2	1
Total	8	2*

TABLE III. *Onset of block (mean (SD))*

	Air group (min)	Saline group (min)
Right	10.5 (5.0)	9.8 (3.3)
Left	8.0 (3.3)	8.5 (2.9)

TABLE IV. *First segment to be blocked (median (range))*

	Air group	Saline group
Right	T11 (T6–L3)	T11 (T8–L1)
Left	T12 (T6–L3)	T11 (T8–L1)

There was no significant difference in the time to onset of the block between the groups on either the right or left side (table III), or in the first segment to be blocked on either side (table IV).

The range of first segment blocked was wider in the air group compared with the saline group, but this was not significant. There was also no significant difference between the groups on comparing the right and left sides in the number of segments blocked at any of the times tested although, as expected, there was a difference within the groups in the number of blocked segments on the right or left side (table V).

The height of the block was comparable also between the two groups (table VI).

DISCUSSION

Since the advent of extradural analgesia, many methods have been proposed to identify the extradural space. The majority of methods rely on

TABLE V. *Number of segments blocked at times* t+15, t+25 *and* t+30 *min (mean* (SD)). $^{*}P < 0.05$; $^{**}P < 0.01$ *within groups*

Time	Air group	Saline group
t+15		
Right	5.7 (3.2)	4.9 (2.5)
Left	7.3 (3.7)	8.1 (3.7)*
t+20		
Right	7.3 (2.7)	7.3 (3.3)
Left	9.4 (3.2)	9.8 (3.7)
t+25		
Right	8.6 (2.5)	8.6 (3.4)
Left	10.6 (3.2)**	10.9 (3.5)**
t+30		
Right	9.4 (2.6)	9.3 (3.5)
Left	10.9 (3.3)	11.5 (3.4)

TABLE VI. *Height of block established at times* t+15, t+20, t+25 *and* t+30 *min (median (range))*

Time	Air group	Saline group
t+15		
Right	T10 (T6–L2)	T10 (T7–T12)
Left	T9 (T6–L2)	T9 (T6–T12)
t+20		
Right	T8 (T5–L2)	T9 (T6–T12)
Left	T8 (T4–L1)	T8 (T5–T12)
t+25		
Right	T8 (T4–L2)	T9 (T5–T12)
Left	T8 (T4–L1)	T8 (T4–T12)
t+30		
Right	T8 (T4–L2)	T9 (T5–T12)
Left	T8 (T4–L1)	T8 (T4–T12)

the identification of the negative pressure in the extradural space or the loss of resistance encountered on entering the space. The technique used most widely today involves loss of resistance detection with either a saline or air filled syringe. There are advantages and disadvantages to each technique.

The advantages of using saline include the fact that a rigid liquid-filled system is ideal for providing a crisp and unequivocal end-point to the loss of resistance test. Liquid is incompressible and so the transition from complete resistance to loss of resistance is immediate and convincing. The distension of the extradural space with saline may aid the passage of a catheter, but an excess of saline may also dilute the local anaesthetic solution and result in inadequate block [1]. The other potential disadvantages of using saline include inability to detect a sticky plunger [2] and difficulty and delay in detecting a dural puncture [3].

Air is compressible, so that detection of the extradural space is more difficult and false positives are possible [4]. In practised hands, however, it does provide an easy and reliable technique, particularly if glass syringes are used [5], and there is no delay or difficulty in detecting dural puncture. Disadvantages of using air include the possibility of missed segments [6], venous air embolism [7] or cervical subcutaneous emphysema if large volumes of air are injected into the extradural space [8].

The frequency of missed or unblocked dermatomal segments during established extradural analgesia for obstetric patients is thought to be about 6–8% [9]. This is similar to the frequency of missed segments in our saline group. There was a much greater incidence in our air group (32%) following the initial dose of bupivacaine. In every subject in our study, the unanaesthetized dermatome was blocked by additional doses of bupivacaine. The mechanism of unblocked segments is unknown, but thought to be caused by either failure of the local anaesthetic solution to reach a given segment in an adequate concentration, or a quantitative increase in afferent input through one or more segmental nerves, possibly by stretching of the round ligament [6]. There are several potential factors to impede the local anaesthetic solution reaching segmental nerves, including malposition of the extradural catheter tip [10], the type of catheter used [11], the presence of extradural membranes and adhesions [12] and distended extradural veins [6].

In this prospective study, our technique was standardized; closed-end (three lateral holes) extradural catheters were used and the patient was maintained in the left lateral position throughout so as to minimize the known experimental variables. A volume of 4 ml of air or saline was chosen following a consensus view amongst local obstetric anaesthetists that 4 ml may be injected easily during identification of the extradural space although this volume was unlikely to be exceeded in experienced hands.

The results of this study indicate that air introduced into the extradural space may significantly increase the incidence of local anaesthetic failing to reach the nerve roots, presumably by the formation of bubbles. The range of first segment to be blocked was wider in the group of patients in which air was used. It is also interesting to note the effect of gravity, with more unblocked segments occurring on the right (uppermost) side. The possibility of bubbles of air collecting within the extradural space following use of air with the loss of resistance technique was realized by Macintosh [5] and confirmed recently by Dalens, Bazin and Haberer [13]. They correlated the formation of air bubbles (as seen in peridurograms) with unanaesthetized segments in extradural block in children. It is debatable if this is relevant to obstetric analgesia, as the extradural space in children extends along spinal nerves which may facilitate significant bubble trapping and, while the volume of air used was unspecified, it is likely that relatively more air was used compared with the size of the infant extradural space.

A study in which 12 ml of air was injected into the extradural space of patients in labour reported no segmental defect in subsequent analgesia, but no details were given [14]. The results of our study are not in disagreement, as they do not show that using air in the loss of resistance technique leads to persistently unblocked segments. We have demonstrated that use of 4 ml of air rather than of saline leads to a greater incidence of patchy analgesia following initial injection of local anaesthetic.

It may be argued that the addition of saline 4 ml had the effect of increasing the volume of local anaesthetic by 50 % whilst maintaining the concentration greater than that required to provide sensory block (0.33 %), and that this was the cause of the smaller incidence of unblocked segments in this group. However, the fact that the characteristics of the spread of the block in the two groups did not differ significantly militates against this. The first segment blocked, the time of onset, the total number of blocked segments and the height of the block were the same. This supports the long held view [15, 16], corroborated recently [17], that the dose of local anaesthetic injected, rather than the volume or concentration, is the important determinant of the subsequent spread of extradural block.

In conclusion, we have demonstrated that the use of air rather than saline to identify the extradural space in labouring patients increased the incidence of unblocked segments following the initial injection of local anaesthetic, but that there was no significant difference in the spread of analgesia.

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EFFECT OF ADRENALINE ON PLASMA CONCENTRATIONS OF BUPIVACAINE FOLLOWING LOWER LIMB NERVE BLOCK

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SUMMARY

Twenty-two patients undergoing total knee arthroplasty received combined sciatic plus femoral "3 in 1" blocks as adjuncts to general anaesthesia. Eleven patients received 0.375% bupivacaine 45 ml (168.75 mg) with adrenaline 1 in 200000 and the remaining 11 received plain solution according to a previously prepared, randomized list. The mean maximum plasma bupivacaine concentration was significantly greater with plain solution than when adrenaline was added (1.66 µg ml^{-1} compared with 0.98 µg ml^{-1}) ($P < 0.05$). Bupivacaine concentrations were greater at all times in the plain group compared with the group receiving adrenaline. These differences were statistically significant at 10, 15 and 20 min ($P < 0.05$). The greatest peak concentration recorded was 3.13 µg ml^{-1} in one patient receiving plain bupivacaine. No patient developed signs of systemic toxic effects. Peak plasma concentrations were related inversely to body weight in patients receiving solution containing adrenaline ($P < 0.005$), but no relationship existed in patients who received plain solution.

KEY WORDS

Anaesthetic techniques, regional. femoral, sciatic. Anaesthetics local· bupivacaine Pharmacokinetics· bupivacaine, adrenaline

Local analgesia of the lower limb using combined sciatic plus "3 in 1" femoral blocks is an established technique used at our hospital. The blocks are an adjunct to light general anaesthesia, and this balanced technique is used for major surgery to the lower limbs. It provides 12–36 h of postoperative pain relief, much longer than that provided by a single-shot spinal or extradural technique, and we have found this is of particular value in patients who are placed in the passive knee mobilizer after joint replacement and who would otherwise require frequent large doses of opioid analgesics. However, a large volume of solution (40–45 ml) of moderately high concentration of local anaesthetic is required for the technique to be effective. Therefore it was decided to study the plasma concentrations of bupivacaine after combined sciatic and femoral "3 in 1" block with and without adrenaline.

MATERIALS AND METHODS

Patients and samples

Patients undergoing prosthetic knee arthroplasty, aged 18–75 yr, gave informed consent to the study. The local Area Ethics Committee approved the study. Patients with evidence of significant cardiorespiratory disease, or impaired hepatic or renal function were excluded. Patients were allocated to one of two groups according to a previously prepared, randomized list to receive either a total volume of 45 ml of 0.375% bupivacaine, or the same volume of solution prepared freshly with adrenaline 1 in 200000.

Premedication was with oral diazepam 10 mg 90 min before operation. Anaesthesia was induced with either methohexitone 1–1.5 mg kg^{-1} or thiopentone 4–6 mg kg^{-1}; suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation if this was considered necessary. Anaesthesia was maintained with nitrous oxide, oxygen and enflurane.

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TABLE I. *Patient and anaesthetic characteristics for the groups receiving plain and adrenaline-containing solution (median (range) or mean* (SD))

	Plain	Adrenaline
Age (yr)	65 (25–71)	65 (38–75)
Weight (kg)	62 (12)	66 (14)
Duration of anaesthesia (min)	127 (36)	117 (19)
Tourniquet time (min)	98 (32)	101 (29)
Block to tourniquet inflation (min)	32 (24)	36 (31)

Ventilation was spontaneous in all patients. The ECG was monitored continuously and systemic arterial pressure was recorded at 5-min intervals for the duration of anaesthesia.

After induction of anaesthesia, a cannula was inserted into a vein at the antecubital fossa for blood sampling. The sciatic block was performed first using the supine technique described by Raj and colleagues [1]. Fifteen millilitre of solution was injected through a 22-gauge Whitacre spinal needle, the start of the injection being designated time 0. Following this, 30 ml of solution was injected into the femoral sheath via a 22-gauge beaded regional block needle to perform the "3 in 1" block [2]. Accurate localization of the peripheral nerves was facilitated using a peripheral nerve stimulator (Bard 750 digital). The blocks were performed in all patients by one of two authors (D.W.McK. or A.S.B.). Surgery was performed under tourniquet on the thigh, inflated to a pressure of 400 mm Hg immediately before skin incision.

Ten millitre of venous blood was withdrawn into lithium–heparin tubes at times 0, 5, 10, 15, 20, 25, 30, 45, 60 and 120 min for measurement of plasma concentration of bupivacaine. Plasma was separated by centrifugation and stored at −20 °C. The sample was prepared by solvent extraction at pH 13 before analysis was performed by high pressure liquid chromatography on reverse phase with ultraviolet detection at 205 nm (limit of detection 0.05 μg ml^{-1}).

Statistical analysis

Differences between the groups in age, weight, duration of anaesthesia, duration of tourniquet inflation and the time from performing the blocks to initial tourniquet inflation were assessed by Student's *t* test. Comparison of plasma concentrations of bupivacaine was by analysis of variance. Correlation of peak plasma concentration of bupivacaine and age and weight of the patient was by Spearman's rank coefficient.

RESULTS

We studied 22 patients; in 11 (five male) plain local anaesthetic solution was used, while the other 11 (four male) received local anaesthetic with adrenaline. The blocks were considered satisfactory in 19 patients; in three the sciatic block was incomplete. No significant differences between the groups were observed with regard to age, weight, duration of anaesthesia, duration of tourniquet inflation and time from performing the blocks to initial tourniquet inflation (table I).

The plasma concentration in the group receiving adrenaline was significantly smaller at 10, 15 and 20 min than in the plain group ($P < 0.05$ for each time) (table II). The mean peak plasma concentration was significantly greater in

TABLE II. *Mean* (SD) *and maximum plasma concentrations of bupivacaine* (μg ml^{-1}) *following sciatic plus femoral "3 in 1" blocks with and without adrenaline.* *P < 0.05 *compared with mean plasma concentration of bupivacaine in plain group*

	Time (min)								
	5	10	15	20	25	30	45	60	120
Plain									
Mean	0.14	1.07	1.30	1.41	1.44	1.46	1.48	1.43	1.20
SD	0.21	0.76	0.79	0.86	0.88	0.80	0.72	0.70	0.60
Maximum	0.67	2.15	2.62	2.76	3.13	2.99	2.35	2.71	2.07
Adrenaline									
Mean	0.04	0.21*	0.48*	0.60*	0.65	0.74	0.82	0.84	0.94
SD	0.08	0.21	0.27	0.39	0.54	0.62	0.63	0.59	0.72
Maximum	0.28	0.53	1.01	1.46	1.96	2.30	2.32	2.08	2.06

the plain group than that in the adrenaline group (1.66 μg ml^{-1} compared with 0.98 μg ml^{-1}) ($P < 0.05$). The addition of adrenaline delayed the attainment of peak concentrations from about 30 min with plain solution to between 60 and 120 min. The plasma concentration of bupivacaine did not exceed 4 μg ml^{-1} in any patient.

The maximum plasma concentration of bupivacaine irrespective of time was related inversely to body weight in patients receiving solution containing adrenaline ($P < 0.005$). No significant relationship existed between weight and peak plasma concentration of bupivacaine in the group receiving plain solution. There was no correlation between the peak plasma concentration and the ages of the patients in each group. None of the patients demonstrated any adverse reaction attributable to the blocks and no patient showed appreciable alterations in heart rate, arterial pressure or cardiac rhythm.

DISCUSSION

Astra Pharmaceuticals Limited, the U.K. manufacturer of bupivacaine, recommend a maximum single dose of bupivacaine 150 mg, based on experience to date. We administered 168.75 mg to all patients in the present study. This did not result in plasma concentrations greater than the predicted toxic concentration of 4 μg ml^{-1} [3], the greatest recorded plasma concentration being 3.13 μg ml^{-1}, and no patient showed signs of toxic effects. All patients received general anaesthesia throughout the period of blood sampling for plasma bupivacaine concentrations and it is possible that this would conceal signs of overt CNS toxicity. The average peak plasma concentration in the group receiving plain bupivacaine was 1.66 μg ml^{-1}, and 0.98 μg ml^{-1} when adrenaline was added. These concentrations compare favourably with those of a previous study [4] in which a mean peak plasma concentration of 1.6 μg ml^{-1} was found in patients given 0.5% bupivacaine 80 ml with 1 in 320000 adrenaline in similar combined sciatic plus femoral "3 in 1" blocks. The implication is that the dose of bupivacaine that we used is acceptable for this combined local anaesthetic technique.

In the present study, peak plasma concentrations of bupivacaine occurred after 30–45 min for plain solution and 60–120 min for the solution containing adrenaline. Indeed, four of the 11 patients receiving solution containing adrenaline may not have developed peak concentrations even by 120 min. This is at variance with an earlier study in which peak concentrations were attained within 15 min [4]. There are at least two possible explanations for this difference. First, the much greater total dose and volume administered in that study may have led to a larger bolus of local anaesthetic being delivered systemically, resulting in the earlier attainment of peak concentrations. Second, the concentration of adrenaline used by Moore and colleagues [4] is less effective in reducing vascular absorption than the 1 in 200000 concentration we used [5].

It is debatable if the addition of adrenaline to the local anaesthetic solution confers any clinically relevant advantage over the use of plain solution. We did not undertake any formal assessment of analgesia in the present study and so cannot comment if adrenaline prolongs the duration of block in this combined approach. Although the mean peak plasma concentrations of bupivacaine in both groups were considerably smaller than the reported toxic concentration, five patients receiving plain solution, but only two receiving adrenaline, exhibited peak concentrations in excess of 2 μg ml^{-1}. Scott [6] has shown previously that systemic toxic effects can result with a mean peak concentration of 2.24 μg ml^{-1} in awake volunteers. In an earlier study [3], volunteers reported slight numbness in the eyelids when infused i.v. with bupivacaine 1.25 mg kg^{-1} over 20 min (mean plasma bupivacaine concentration 2.1 μg ml^{-1}). The often quoted [4, 7–9] toxic concentration of 4 μg ml^{-1} in man is hypothetical, as it is predicted from studies in dogs. Because this is the concentration at which convulsions, rather than subjective feelings of toxicity, might be expected to occur, it may be that the addition of adrenaline does protect against the development of potentially toxic blood concentrations. No patient receiving adrenaline in the present study showed appreciable changes in heart rate or arterial pressure. On the basis of these findings, it is now policy in our hospital to use adrenaline-containing solution for this combined block.

The principal factor in determining local anaesthetic toxic dosage is probably the vascularity of the site of injection and the possibility of intravascular injection. It is thought that sciatic–femoral blocks represent a low risk for inadvertent intravascular injection [4]. Other factors such as age and weight have been said to influence development of systemic toxic reactions [5]. Our results suggest that weight might be a predictor of toxicity only in patients receiving solution containing adrenaline, but confirm the previous finding that age of the patient does not correlate with peak plasma concentration of bupivacaine [10].

Several authors have described local anaesthetic techniques using a larger dose of bupivacaine than the manufacturer recommends. In a series of 11080 regional nerve blocks using doses of up to 600 mg with adrenaline, Moore and colleagues found only 15 patients with systemic toxic effects [11]. Touminen, Rosenberg and Kalso [12], studying axillary nerve block, administered bupivacaine in doses greater than 3 mg kg^{-1} and reported no toxic effects and a greatest plasma concentration of 3.3 μg ml^{-1}. In a further study, Neill and Watson [8] demonstrated that, although a mean dose of bupivacaine 3.4 mg kg^{-1} resulted in mean peak concentrations of 4.95 μg ml^{-1} without adrenaline and 3.56 μg ml^{-1} with adrenaline, no systemic toxic effects were apparent. This reinforces the notion that the maximum safe total dose of local anaesthetic varies and depends upon the area to be anaesthetized, the vascularity of the tissues, individual tolerance and the technique of anaesthesia used.

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COMPARISON OF INCREMENTAL SPINAL ANAESTHESIA USING A 32-GAUGE CATHETER WITH EXTRADURAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION

I. G. KESTIN, A. P. MADDEN, J. T. MULVEIN AND N. W. GOODMAN

SUMMARY

Forty-three mothers who had requested regional anaesthesia for elective Caesarean section were allocated randomly to receive either extradural anaesthesia with pH-adjusted 2% lignocaine with 1/200000 adrenaline, or incremental spinal anaesthesia using a 32-gauge catheter with 0.5% plain bupivacaine. Increments of lignocaine or bupivacaine were given with the aim of achieving a block from T4 to S5. The spinal catheter was quicker to place (median 3 min, range 1–45 min, compared with median 10 min, range 1.5–50 min) and spinal anaesthesia was quicker to establish (median 20 min, range 10–46 min compared with median 48 min, range 15–59 min) compared with the extradural technique. The maximum height of the spinal block was significantly higher (median T3–4, range T5–T3) than the extradural group (median T5, range T6–T3). The total dose of intrathecal 0.5% bupivacaine was unpredictable, with a mean dose of 2.7 ml and a range between 1.5 ml and 7.4 ml. Haemodynamic stability and the quality of the block were similar between the groups. There were two mild spinal headaches in the spinal group. All the spinal catheters were removed intact.

KEY WORDS

Anaesthesia obstetric Anaesthetic techniques: extradural, spinal

Spinal anaesthesia has some advantages over extradural anaesthesia for Caesarean section. It is technically easier to perform and can be performed more quickly; the block is more rapid in onset and is more reliable. Only small doses of local anaesthetics are used, so there is little systemic absorption by mother and fetus and no risk of large doses of local anaesthetic being administered into a vein or the subarachnoid space.

The disadvantages of spinal anaesthesia by single injection are unpredictable spread (with no chance, unless a combined extradural–spinal technique is used, of giving more injections to extend an inadequate block or for postoperative analgesia), the rapid onset of hypotension and the risk of spinal headache.

An incremental technique through a spinal catheter may overcome some of these disadvantages while retaining the advantages, and the incidence of spinal headache may be lower if a spinal catheter has been used [1]. This study was a single-blinded (patient) stratified randomized trial of two regional techniques for elective Caesarean section: extradural anaesthesia, and spinal anaesthesia using a 32-gauge catheter (TFX Medical).

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. Forty-three consecutive mothers who had requested regional anaesthesia for elective Caesarean section gave written informed consent, and they were allocated randomly to receive either extradural anaesthesia, or spinal anaesthesia using a 32-gauge catheter. Randomization was stratified: mothers who had had a previous Caesarean section under regional anaesthesia were randomized separately. We excluded from the study

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mothers with a multiple pregnancy, diabetes, cardiorespiratory disease or a fetus of less than 38 weeks of gestational age. All mothers were visited before operation by one of the authors (I.G.K.) and received a standard explanation of the study and anaesthesia. The mothers were given oral ranitidine 150 mg the night before and 2 h before surgery. All the anaesthetics and assessments were made by I.G.K. or A.P.M. In the anaesthetic room, a 14-gauge i.v. cannula was inserted using local anaesthesia, and the mother turned onto her left side.

Extradural anaesthesia

A 16-gauge Tuohy needle was inserted at L3–4 in the midline and the extradural space identified by loss of resistance to air. Approximately 3 cm of catheter was inserted into the extradural space. The mother was then turned onto her back, sitting semi-upright with 20° of left lateral tilt. I.v. crystalloid 15 ml kg^{-1} was given before the test dose of 2 ml of pH-adjusted 2% lignocaine with 1/200000 adrenaline (preservative-free 8.4% sodium bicarbonate 2 ml and 1/1000 adrenaline 0.1 ml were added to 2% lignocaine 20 ml just before use). This lignocaine solution was used for the main dose and all subsequent doses. The initial dose of 10–13 ml of solution was given 5 min after the test dose. After 15 min, the mother was placed supine with 20° of left tilt, and the block assessed by loss of segmental sensation to cold. The block was reassessed at 3–5-min intervals until surgery. Increments were given of 1–1.5 ml of solution for each unblocked segment below T4 if two successive measurements were at the same segmental level. The aim was a bilateral block from T4 to S5.

Spinal anaesthesia

We checked that each spinal catheter would pass through the spinal needle before performing the lumbar puncture. The 32-gauge catheter passed easily down all 26-gauge Becton Dickinson needles. An oblique paraspinous approach was used, with a 26-gauge or 27-gauge needle at L3–4 with the bevel facing laterally. Three centimetre of catheter was threaded into the subarachnoid space. The mother was then turned supine with 20° of left lateral tilt, and i.v. crystalloid 20 ml kg^{-1} given before the first injection of plain 0.5% bupivacaine 1.5 ml. A larger loading volume was given to the patients having spinal anaesthesia because of the more rapid onset of hypotension. The block was assessed after 10 min by loss of segmental sensation to cold, and reassessed at 3-min intervals until surgery. Increments of 0.2–2 ml of 0.5% bupivacaine were given if two successive measurements were at the same segmental level, with the aim of achieving a bilateral block from T4 to S5.

Monitoring

The time to place the catheter (time from first insertion of the Tuohy needle or spinal needle to time of removing the needle over the catheter) and the time to establish a block sufficient for surgery (from the time of the first injection of local anaesthetic) were recorded by an independent observer. Arterial pressure and heart rate were measured with a non-invasive automated recorder (Critikon Dinamap) at 3-min intervals during the onset of the block. I.v. ephedrine was given if the systolic pressure was less than 100 mm Hg or had decreased by more than 20 mm Hg between successive readings. The mothers were asked immediately after surgery, and again at 24 h, to rate their discomfort during surgery as none, mild, moderate or severe. The presence of nausea and vomiting and concurrent hypotension or surgical stimuli were noted. Daily postoperative visits were made for 4 days, to enquire about headache, backache and neurological sequelae. All the spinal catheters were removed in the recovery ward by the investigators.

Data were analysed by Mann–Whitney *U* test (time to place catheter and establish block, maximum height of the block and Apgar scores), unpaired *t* test (age, weight, height and dose of ephedrine) and chi-square contingency table with Yates' continuity correction (incidence of nausea and vomiting, motor block, hypotension, discomfort during surgery and use of ephedrine). A probability of less than 5% was taken as statistically significant.

RESULTS

There were no significant differences between the groups in age, height, or weight ($P = 0.07$) (table I). Two mothers in the spinal group were withdrawn from the study: the subarachnoid space could not be identified in one patient, and the catheter could not be threaded in the other. One of the mothers in the extradural group had a catheter resited at L2–3 because an extradural vein was entered at L3–4. Another mother in the

TABLE I. *Patient characteristics (mean (range or SD)) and anaesthetic data (median (range)).* *P < *0.05*, **P < *0.01*

	Age (yr)	Weight (kg)	Height (cm)	Time to place catheter (min)	Time to establish block (min)
Extradural (*n* = 20)	28.2 (23–35)	77.9 (12.6)	162 (8.9)	10 (1.5–50)	48 (15–59)
Spinal (*n* = 20)	28.4 (18–36)	71.2 (11.0)	160 (7.2)	3* (1–45)	20** (10–46)

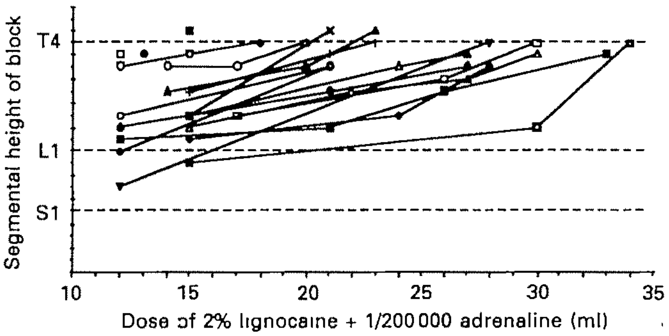

FIG. 1. Individual dose–response curves. segmental height of block *vs* dose of pH-adjusted 2% lignocaine+adrenaline 1/200000, for extradural anaesthesia for Caesarean section.

extradural group was withdrawn from the study and given a general anaesthetic soon after skin incision because of severe discomfort.

The block could not be extended to T4 in all the mothers in the extradural group; for 10 of the 20 patients the maximum dose of local anaesthetic had been given. The maximum height of the block in the spinal group (median T3–4, range T5–T3) was significantly higher ($P < 0.002$) than the maximum height in the extradural group (median T5, range T6–T3). Two of the extradural blocks were only just satisfactory for surgery—these two patients were given i.v. fentanyl after delivery. All the other extradural and spinal blocks were satisfactory for surgery without supplementation. Two patients in the spinal group complained of pain at the site of surgery soon after skin closure, and were given an increment of 1 ml of intrathecal bupivacaine before the catheter was removed. The mean dose of lignocaine solution used for extradural block was 22.7 (range 12–34) ml (fig. 1).

The spinal technique was quicker to perform and a satisfactory block was achieved significantly faster (table I). Haemodynamic stability and the quality of the block were similar in the two groups (tables II, III). There was no difference in fetal outcome measured by the 5-min Apgar score. The ratings of discomfort by the patients were the same immediately after surgery and at 24 h.

TABLE II. *Adverse effects of incremental spinal anaesthesia compared with extradural anaesthesia for Caesarean section*

Number of patients with	Extradural (*n* = 20)	Spinal (*n* = 20)
Mild discomfort during surgery	4	6
Moderate discomfort during surgery	4	1
I v supplementation of analgesia during surgery	2	0
Nausea/vomiting with surgical stimuli	7	7
Complete motor block	7	8

The mean dose of intrathecal bupivacaine was 2.7 (range 1.5–7.4) ml (fig. 2). The maximum height of the block was from T3 to T5 with the incremental technique. There was no relationship between the dose of intrathecal bupivacaine and the patient's experience of pain during surgery. The mean dose of intrathecal bupivacaine in the

TABLE III. *Haemodynamic stability of incremental spinal anaesthesia compared with extradural anaesthesia for elective Caesarean section: systolic arterial pressure (SAP) and requirement for ephedrine (mean (range))*

	Extradural ($n = 20$)	Spinal ($n = 20$)
Number of patients with SAP < 100 mm Hg	10	8
Number of patients with SAP < 80 mm Hg	3	2
Number of patients given ephedrine	12	10
Dose of ephedrine (mg)	16.4 (6–30)	16.8 (6–45)

seven patients who experienced some pain during the operation was 2.3 (range 1.5–3.3) ml, and two patients had a complete motor block.

Four patients in the spinal group complained of headache at some time during the first 4 days after operation and two patients described symptoms typical of dural puncture. The onset of headache in these two mothers was 24–48 h after operation, and they lasted 2 and 3 days. Both mothers described the headaches as mild; they did not have to restrict movements and they required only oral analgesics.

Three patients who had an extradural block complained of headache at some time in the first 4 days after operation, but none was typical of dural puncture. Five patients who had had a spinal block and four patients who had had an extradural block had non-specific backache at some time after operation. There were no neurological sequelae in any of the patients when last questioned at 4 days. All the spinal catheters were removed intact.

DISCUSSION

The incremental technique of spinal anaesthesia was quicker, and produced a satisfactory block more quickly, than extradural anaesthesia. However, in this study there were some patients in whom the subarachnoid space was difficult to find, and some patients who needed several increments of intrathecal bupivacaine and in whom the block was relatively slow in onset. Otherwise, the two techniques were similar. In their textbook, Moir and Thorburn wrote "The quality of analgesia may be rather greater with subarachnoid block" [2]. In this study, the quality of the incremental spinal block was not better than that of the extradural block; there was no difference in the patients' rating of discomfort during surgery, nausea and vomiting with surgical stimuli, or the incidence of complete motor block.

Two of the 20 patients had spinal headaches—the expected incidence in obstetric patients after a 26-gauge spinal puncture [3]. Denny and colleagues reported an unexpectedly low incidence of headache, even after using a 20-gauge intrathecal catheter [1]. A study of the true incidence of headache with 32-gauge catheters would require a large number of patients but, if confirmed, would be a worthwhile additional clinical advantage of using an intrathecal catheter.

In spinal anaesthesia by single injection, the height of the block is variable in pregnant patients [4]. In our study, the dose was variable, but the height of the block was well controlled within a narrow range of segments by the incremental technique. There is one important difference between spinal anaesthesia by single injection and this technique of incremental spinal anaesthesia. After single-injection spinal anaesthesia, moving

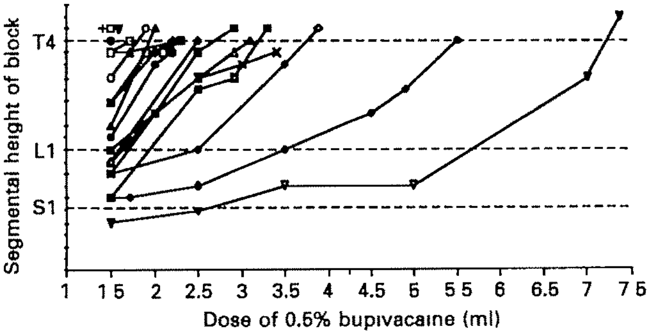

FIG. 2. Individual dose-response curves: segmental height of block *vs* dose of 0.5% bupivacaine, for incremental spinal anaesthesia through a 32-gauge catheter for Caesarean section.

the patient from lateral to supine causes cephalad extension of the block [5]; with the incremental technique, all doses of intrathecal bupivacaine can be given through the catheter after the patient has been positioned for surgery. The only subsequent movement of the patient, during insertion of the urinary catheter, did not cause cephalad extension of the block in our study. If the incremental technique is used with the patient *already* supine and there is need for subsequent movement of the patient (for example, to treat aortocaval compression), this might cause further unpredictable extension of the block.

We found 1.5 ml of 0.5% plain bupivacaine was too large as an initial dose: three patients had a sensory level at T3 after this dose. *Once the block is established*, we suggest an increment of 1.5 ml of 0.5% plain bupivacaine if the sensory level is in the sacral segments; 1 ml if the sensory level is still in the lumbar segments; and 0.25–0.5 ml if the sensory level is in the low thoracic segments. From our results, we should surmise that these increments should not extend the analgesia to dangerously high levels. The spread of spinal anaesthesia after a single injection is more variable in pregnant patients than in general surgical patients [6], and the reason for this is not fully understood. This seems to be true also of incremental spinal anaesthesia; there was less variability in a group of general surgical and urological patients [7].

Hurley and Lambert reported technical difficulties with the prototype 32-gauge spinal catheter [8]. These were mainly difficulty in threading the catheter (30%) or breakage. In our study, we had difficulty with the catheter in only one of 22 patients. However, there had been more failures in an earlier pilot study [7]. We recommend that anaesthetists learn to use the 32-gauge catheters in elderly patients, who are less likely to suffer spinal headache after dural puncture.

In our study, the assessor of the heights of the blocks was not blinded to the anaesthetic method. It would be difficult to organize a truly double-blind trial because of the different time intervals and speed of onset between the two techniques.

Within the constraints of not being a double-blind trial, we have shown that an incremental technique of spinal anaesthesia using a 32-gauge catheter is easier and quicker than extradural anaesthesia for elective Caesarean section. Once experience in the technique has been gained, the 32-gauge catheter is usually easy and quick to insert. Although the total dose of intrathecal bupivacaine is variable, the maximum height of the block may be controlled within a narrow range of segments. The height of the block may always be extended with the spinal technique; with extradural anaesthesia 50% of patients in our study had to be given their maximum dose of local anaesthetic. Haemodynamic stability and the quality of block were similar in the two groups. The only adverse effect of the technique was mild spinal headache in two patients, although further studies with larger numbers of patients will be needed to determine if spinal headaches are an important clinical problem with the 32-gauge catheter.

ACKNOWLEDGEMENT

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British Journal of Anaesthesia 1991; **66**: 237–241

EXTRADURAL CLONIDINE DOES NOT POTENTIATE ANALGESIA PRODUCED BY EXTRADURAL MORPHINE AFTER MENISCECTOMY

E. J. VAN ESSEN, J. G. BOVILL AND E. J. PLOEGER

SUMMARY

We have studied the ability of clonidine to potentiate morphine analgesia in 28 patients (ASA I) after meniscectomy under general anaesthesia. One hour after surgery, morphine 3 mg ($n = 10$), clonidine 75 µg ($n = 8$) or morphine 3 mg plus clonidine 75 µg ($n = 10$) was injected extradurally. Morphine alone and in combination with clonidine produced similar and significant analgesia as assessed by verbal analogue pain scores. Pain scores did not decrease significantly in patients given clonidine alone. There were statistically, but not clinically significant decreases in systemic arterial pressure after morphine alone and clonidine alone. No patient developed sensory or motor block. One patient given morphine alone developed retention of urine. It is concluded that, in the dose used in this study, clonidine did not potentiate the analgesia produced by extradural morphine.

KEY WORDS

Anaesthetic techniques: extradural. Analgesics morphine, clonidine.

Clonidine is a partial α_2-adrenoceptor agonist that produces analgesia when administered systemically, intrathecally and extradurally [1–3]. Analgesia produced by clonidine and other α_2-adrenoceptor agonists is independent of the endogenous opioid system, as it is not antagonized by naloxone [4–6], but is antagonized by the α_2-antagonist yohimbine [7]. Nonetheless, there is evidence for interactions between the two systems. Supraspinally administered morphine results in the release of noradrenaline within the spinal cord [8, 9]. In the rat, yohimbine attentuates the antinociceptive effect of both clonidine and morphine [10]. Antinociceptive interactions between opioids and α_2-adrenoceptor agonists at the spinal cord level in rats have been demonstrated [6, 11, 12]. This suggests that the spinal administration of a combination of an α_2-adrenoceptor agonist and an opioid should produce greater analgesia than each alone. This would be beneficial in reducing dose requirements and thus the risk of side effects from both drugs.

Clonidine potentiates the analgesia produced by morphine in animals [6, 12, 13]. The combination of clonidine and morphine extradurally given 18 h after surgery to patients who had undergone oesophagogastrectomy resulted in a potentiation of the intensity, but not the duration of analgesia [14]. The purpose of our study was to determine if a similar interaction exists between extradurally administered clonidine and morphine in patients with pain after knee surgery.

PATIENTS AND METHODS

Twenty-eight patients, ASA class I, undergoing arthroscopy followed by arthrotomy with meniscectomy under general anaesthesia, participated in the study, which was approved by the local medical Ethics Committee. Informed written consent was obtained from each patient. None of the patients was taking analgesics before operation.

All patients were given atropine 0.5 mg i.m. 30 min before arriving in the operating theatre. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen and halothane to a maximum

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inspired concentration of 2%. Patients breathed spontaneously via a face mask throughout anaesthesia. During anaesthesia the ECG and heart rate were monitored continuously and systemic arterial pressure recorded non-invasively (Dinamap) at 5-min intervals. During surgery Ringer's solution was infused at a rate of 5–7 ml kg^{-1} h^{-1}. At the end of surgery, anaesthesia was discontinued and the patient transferred to the recovery room.

In the recovery room patients were allocated at random to one of three groups, using a computer-generated table of random numbers. One hour after the end of surgery a Tuohy needle was inserted into the extradural space at the L2–3 interspace and a test dose of lignocaine 2 ml with adrenaline 5 μg ml^{-1} injected. Then morphine sulphate 3 mg in saline 10 ml (group I), morphine sulphate 3 mg plus clonidine 75 μg in saline 10 ml (group II) or clonidine 75 μg in saline 10 ml (group III) was injected, and the needle withdrawn. The drugs were prepared by a nurse who took no further part in the study. Drugs were administered by one of the investigators (E.v.E.) who was unaware of the drug given. He was responsible also for all observations during the study.

Pain, pinprick and touch sensation, motor power and ventilatory frequency were recorded before and 30, 60, 90, 120, 180, 240, 300 and 360 min after drug administration. Pain was assessed using a verbal analogue scale: patients were asked to state the degree of pain on a scale from 0 (no pain) to 10 (worst possible pain). Pinprick and touch sensation were compared between the area around the knee of the non-operated leg and the shoulder area. They were classified as positive if sensation at the knee was less than that at the shoulder. Motor power was assessed by asking the patient to bend the knee on the non-operated side against pressure applied by the observer. This was recorded as unchanged (compared with pre-drug power), diminished or absent. ECG and heart rate were monitored continuously and arterial pressure recorded non-invasively (Dinamap) at 5–15 min intervals.

The occurrence of side effects, in particular urinary retention, nausea or vomiting and pruritis were noted. Escape analgesic medication (piritramide 15 mg i.m.) was given when the patient specifically requested additional analgesia or when the nursing staff, using the routine criteria in the recovery room, judged that this was indicated.

Patient data were compared using unpaired *t* tests. Other data were analysed by two-way analysis of variance for repeated measures. When indicated, differences within and between the groups were compared using a modified *t* test and the Bonferroni correction for multiple comparisons [15]. A value of $P < 0.05$ was considered significant. Data are presented as mean (SD).

RESULTS

Two patients, both allocated to group III, requested to be withdrawn from the study within 10 min of injection of clonidine, and were not included in the subsequent analysis. The reasons for withdrawal were excessive pain and a request for an alternative form of analgesia in one patient and psychological reasons in the other. No other patients were withdrawn after admission to the study.

The three groups were comparable with respect to age, weight and height (table I). The duration of anaesthesia was significantly ($P < 0.05$) longer in group I than in groups II and III.

The pain scores before drug administration

TABLE I. *Patient characteristics (mean (SD))*

	Group I	Group II	Group III
No. patients	10	10	8
Sex (M:F)	9:1	8:2	6:2
Age (yr)	32 (8.0)	32 (12.7)	29 (5.3)
Weight (kg)	77 (8.5)	71 (10.5)	76 (9.9)
Height (cm)	176 (15.1)	174 (8.5)	178 (8.6)
Duration of anaesthesia (min)	74 (15.0)	57 (16.0)	58 (17.0)

TABLE II. *Visual analogue pain scores (mean (SD)) (time = 0) and after extradural administration of morphine 3 mg (group I), morphine 3 mg plus clonidine 75 μg (group II), or clonidine 75 μg (group III).* ** $P < 0.01$ vs time = 0 min; * $P < 0.05$ vs group III; †† $P < 0.01$ vs group III

Time (min)	Group I	Group II	Group III
0	5.5 (2.2)	5.2 (2.2)	5.3 (1.1)
30	4.4 (2.0)	3.1 (1.9)**	4.3 (1.4)
60	3.1 (2.0)	2.8 (2.3)**	4.0 (1.1)
90	2.5 (1.9)**	2.4 (2.1)***	4.5 (1.1)
120	2.2 (1.6)***	2.1 (2.0)***	4.8 (1.4)
180	1.8 (1.4)** ††	2.1 (2.1)***	5.3 (1.7)
240	1.7 (1.5)** ††	1.9 (2.0)** ††	6.3 (1.2)
300	1.8 (1.3)** ††	2.2 (2.2)** ††	6.3 (0.8)
360	2 2 (1.5)** ††	2.5 (2.1)** ††	6.3 (1.0)

were similar between the groups. Pain scores decreased following both morphine alone and the morphine–clonidine combination (table II), but did not differ from the pre-drug score in patients given clonidine alone. Pain scores between groups I and II did not differ. No patient in any of the groups requested or was given rescue medication. Analysis of variance showed that there were no differences between the groups with respect to systemic arterial pressure, heart rate or ventilatory frequency, or within the groups with respect to heart rate or ventilatory frequency. There were, however, significant differences with respect to arterial pressure within groups I and III. In group I (morphine only) systolic and diastolic arterial pressures were significantly ($P < 0.05$) lower at 4 h (systolic 119 (10.4) mm Hg; diastolic 72 (4.3) mm Hg) compared with control values of 132 (9.4) mm Hg and 82 (6.7) mm Hg, respectively. In group III (clonidine only) diastolic arterial pressure was significantly ($P < 0.05$) lower at 60 min (72 (14.2) mm Hg) compared with the control value of 84 (7.8) mm Hg. Systolic arterial pressure did not change in this group. There were no changes in arterial pressure in group II.

No changes in pinprick and touch sensation or in motor power were observed in any patient. No patient developed nausea, vomiting or pruritis. None of the patients became sedated. One patient in group I developed retention of urine which required catheterization of the bladder.

DISCUSSION

In addition to supraspinal modulation of nociception, opioids also regulate the processing of nociceptive information directly in the spinal cord [16]. This action is mediated via specific opioid receptors and results in selective analgesia without motor or sympathetic block [17]. Several other receptor agonists, including adrenergic amines [4], are involved at the spinal cord level in producing analgesia by modulating afferent nociceptive input or its onward transmission to higher centres, or both. There is theoretical and experimental evidence from animal studies that α_2-adrenoceptor agonists potentiate opioid analgesia at the spinal cord level [6, 11–13]. In humans, the combined extradural administration of morphine 50 $\mu g\ kg^{-1}$ and clonidine 2 $\mu g\ kg^{-1}$ resulted in significantly better analgesia than that produced by morphine 50 $\mu g\ kg^{-1}$ alone [14]. However, we found that the combination of extradural clonidine 75 μg and morphine 3 mg did not produce greater analgesia than that produced by morphine 3 mg alone. There are several possible explanations why our results are at variance with those of other investigators.

With the exception of the study by Petit and colleagues [14], all the existing experimental evidence that the two antinociceptive systems potentiate each other has been derived from animal studies, mainly in rats. It is possible that there is a species difference for this effect. However, clonidine and morphine act synergistically to produce analgesia after intrathecal injection in monkeys [5], a species much closer in general to humans. In addition, in most of these studies the drugs were administered intrathecally, and in none of the animal studies were they given extradurally.

Bonnet and colleagues [18] found that a single extradural injection of clonidine 2 $\mu g\ kg^{-1}$ provided satisfactory analgesia (but of short duration) in patients who had undergone perianal procedures or surgery on the knee. However, in that study surgery was performed under local anaesthesia with 2% lignocaine plain solution given via an extradural catheter inserted before operation. In addition, some patients also received general anaesthesia with thiopentone and nitrous oxide. We purposely avoided using an extradural catheter, as we were unable to predict, before operation, which patients would progress from arthroscopy to open meniscectomy. Patients undergoing only arthroscopy generally have only mild pain after operation and we felt that it would have been unethical to subject them to unnecessary cannulation of the extradural space. With the exception of a small test dose of lignocaine with adrenaline, to exclude vascular injection, we avoided the use of local anaesthetics. An interaction between amethocaine and clonidine has been demonstrated in humans [19] and this may also apply for lignocaine. A consequence of our not using large doses of local anaesthetics is that we cannot be absolutely certain that our test drugs were injected accurately into the extradural space. The insertion of the Tuohy needle and the extradural injection were, however, carried out by an anaesthetist with many years experience with the extradural technique. When he had any doubt about the position of the needle, the patient was excluded from the study.

We found that extradural clonidine 75 μg did not result in significant analgesia in our patients. We purposely chose a smaller dose than that used in previous studies in order to test for potentiation. If there is a positive interaction between clonidine and morphine for analgesia this could be either synergistic or additive. In both cases, we should have expected that the response to the combination would be greater than that of morphine alone. This was not the case. It is possible, of course, that our choice of dose of clonidine was too small to allow for potentiation. Direct application of morphine 5–150 µg to the spinal cord produces a dose-related inhibition of C fibre activity by 57%. This response is unchanged in the presence of small doses (10 µg) of clonidine, but larger doses of clonidine (greater than 50 µg) increase morphine-induced C fibre inhibition to 90% [20].

Postoperative pain may not be the most appropriate model for studying potential interactions between clonidine and morphine. Extradural clonidine has been found to be effective in diminishing chronic cancer and non-cancer pain [21, 22]. This latter pain is transmitted mainly by C afferent fibres, whereas the fast Aδ and Aβ fibres are involved predominantly in the transmission of acute, postoperative pain. In the spinal cord, low doses of both morphine and clonidine produce a selective, dose-dependent inhibition of C fibre evoked activity [20, 23]. Aδ and Aβ fibre activity is reduced only slightly by these drugs, and only by the application of high doses. Neither extradural morphine nor extradural clonidine cause significant interruption of transmission in these fast fibres, as assessed by somatosensory evoked potentials [24, 25]. Extradural clonidine 150 µg was considered unsuitable for the treatment of postoperative pain after abdominal hysterectomy [3]. Clonidine 3 $\mu g\ kg^{-1}$ extradurally lacked clinically significant analgesic effects on severe pain following thoracotomy [26]. Extradural clonidine in doses less than 400 µg was relatively ineffective against acute postoperative pain, and doses greater than 600 µg were required for effective analgesia [27]. Such large doses may result in possibly unacceptable haemodynamic changes. However, Eisenach, Lysak and Viscomi [27] found that the degree of hypotension was greatest with intermediate doses of clonidine (400–600 µg) and least following large doses (700–900 µg). This effect is possibly a result of the predominance of the peripheral α_2-adrenoceptor-mediated vasoconstriction with the greater doses [28].

In conclusion, we found that the combination of extradurally administered clonidine in combination with morphine did not result in improved analgesia compared with morphine alone. With the doses used in our study, clonidine did not potentiate the analgesic effects of extradural morphine. Furthermore, extradural clonidine 75 µg alone was unsatisfactory for postoperative analgesia.

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EXTRADURAL DIAMORPHINE WITH ADRENALINE IN LABOUR: COMPARISON WITH DIAMORPHINE AND BUPIVACAINE

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SUMMARY

In a randomized double-blind study of 51 primigravida, we have examined the relative efficacies of bupivacaine, diamorphine or diamorphine with adrenaline given by the extradural route for relief of pain during labour. Group 1 (n = 18) received diamorphine 5 mg in 0.9% sodium chloride 8 ml; group 2 (n = 19) received diamorphine 5 mg in 0.9% sodium chloride 8 ml with 1:200000 adrenaline; group 3 (n = 14) received 0.375% bupivacaine 8 ml. All patients received 0.375% bupivacaine 8 ml as a supplement after the initial analgesia had subsided. Patients in all groups had satisfactory and comparable analgesia 20 min after the initial injection. However, after 60 min and up to 8 h, analgesia was superior in group 2 as assessed by linear analogue pain scores, with statistical significance at 4, 6 and 8 h. Groups 1 and 2 required bupivacaine supplements less frequently than group 3 (P < 0.001). There were no serious adverse effects in any group, but pruritus was a feature in the diamorphine groups. Diamorphine 5 mg may be used as an alternative to bupivacaine 0.375% 8 ml in the first stage of labour and provides a longer duration of action. The addition of adrenaline 1:200000 appears to augment both the quality and duration of analgesia.

KEY WORDS

Anaesthesia: obstetric. Analgesics: diamorphine, extradural. Anaesthetics, local. bupivacaine.

Local anaesthetic agents have achieved widespread acceptance as extradural analgesics in labour, but at the expense of adverse effects, such as hypotension, bradycardia, paraesthesia, motor block and urinary retention. The risk of intravascular injection, more likely in the presence of the extradural venous engorgement of labour, and the possibility of inadvertent intrathecal injection have stimulated research into alternative analgesic techniques.

It has been shown that extradural diamorphine 5 mg, when combined with bupivacaine, provides superior analgesia with fewer bupivacaine supplements in primigravidae in labour [1]. The addition of a vasoconstrictor, such as adrenaline 1:200000, is used commonly to decrease systemic uptake of local anaesthetics from the extradural space. A greater duration of analgesia following Caesarean section was found when adrenaline was added to diamorphine compared with diamorphine in saline [2], both given extradurally.

This study was designed to examine the efficacy of diamorphine as a sole extradural analgesic compared with bupivacaine, and to assess if the addition of adrenaline to diamorphine would be advantageous.

PATIENTS AND METHODS

In a randomized, double-blind trial, we studied 51 primigravid women (ASA I-II) who requested extradural analgesia in labour. Informed consent was obtained and the study was approved by the hospital Ethics Committee. No patient had received opioid analgesia by any route on the day of study.

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TABLE I. *Patient characteristics (mean (SEM or range))*

	Group 1	Group 2	Group 3
Age (yr)	22.25 (17–28)	23.7 (17–32)	24.3 (20–31)
Weight (kg)	78.3 (2 95)	77 (2.94)	75 (3 1)
Duration of labour after extradural (min)	505 (45)	571 (56.4)	449 (56.1)

The drugs were pre-packaged in numbered envelopes and randomized by the hospital pharmacy department using random number tables. Patients received an i.v. preload of compound sodium lactate solution 500 ml before insertion of 3 cm of catheter in either the L2–3 or L3–4 extradural space.

Three groups were studied. Group 1 patients ($n = 18$) received diamorphine 5 mg in 0.9% sodium chloride 8 ml. Group 2 ($n = 19$) received diamorphine 5 mg in 0.9% sodium chloride 8 ml with 1:200000 adrenaline. The adrenaline solution contained also sodium metabisulphite as an antioxidant. Group 3 received 0.375% bupivacaine 8 ml. Supplements of 0.375% bupivacaine 8 ml were given to all patients when analgesia subsided, prior assurance having been given that an effective drug was available if the trial drug was ineffective.

The diamorphine was prepared in the relevant solvent to an 8-ml volume by either an anaesthetic colleague or a senior midwife. The 0.375% bupivacaine was drawn up from a prepared ampoule. The unlabelled syringe was given to the operator.

Initially, the study had been designed to contain 60 patients, 20 in each group. Six women had incomplete records and were unassessable. Three envelopes contained broken ampoules and were discarded.

The attending midwife documented all data except for analgesia. Heart rate and systemic arterial pressure were measured every 5 min for 30 min after each bolus of extradural drug.

Analgesia, sedation, ventilatory frequency, heart rate, arterial pressure and adverse effects such as paraesthesiae, pruritus, urinary retention, motor block, nausea and vomiting were noted. Assessments were made at 0 min (before drug administration) and at 20, 40 and 60 min and 2, 4, 6, 8 and 12 h.

Analgesia was evaluated using a linear analogue scale [3]. On a 10-cm line (one end representing "no pain at all", the other the "worst pain imaginable") patients were asked to mark where they assessed the severity of their pain. Sedation was measured using a four-point sedation scale: 0 = wide awake; 1 = drowsy; 2 = very drowsy; 3 = sleeping. The times taken to require bupivacaine supplements were noted. Fetal state was assessed using the Apgar scoring system.

Results were analysed statistically using one-way analysis of variance, chi-square tests, Yates' correlation, the Logrank test and the F test where suitable.

RESULTS

There were no significant differences between the groups in age, weight and duration of labour under extradural analgesia (table I).

Satisfactory analgesia with comparable pain scores was achieved in all three groups after 20 min. Between 60 min and 8 h, analgesia was superior in group 2, being significant at 4, 6 and 8 h ($P = 0.006$, $P = 0.03$ and $P = 0.04$, respectively) (fig. 1). There were no significant differences between groups 1 and 3.

In groups 1 and 2, there was a significantly longer time to the first bupivacaine supplement ($P < 0.001$) compared with group 3. There was a small but non-significant difference between groups 1 and 2 in this respect (table II).

The mean interval between supplements was significantly less in group 3 compared with groups 1 and 2 (table II) ($P < 0.001$). However, there was no difference between groups 1 and 2.

There was a tendency for both opioid groups to require bupivicaine supplements later than the bupivacaine group, and for group 2 (diamorphine with adrenaline) to require supplements last (fig. 2).

Sedation was greater in the opioid groups, but this was significant only at 20 and 40 min. Peak sedation times occurred at 20 min in the diamorphine group, and at 4 h in the diamorphine with adrenaline group (table III).

Mild hypotension occurred in three group 1 patients and one group 3 patient, in whom systolic

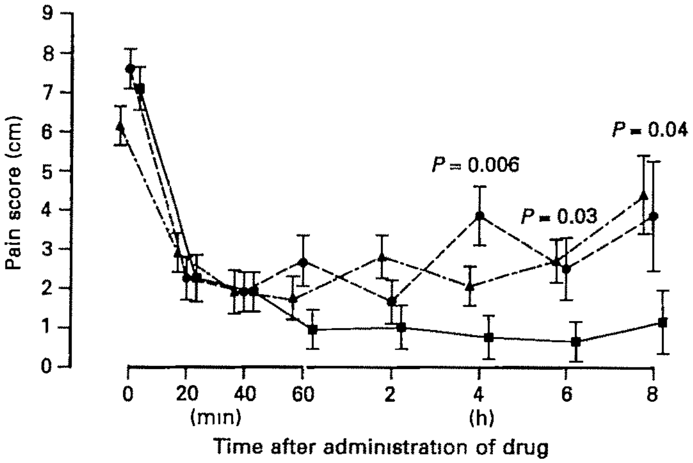

FIG. 1. Linear analogue pain scores (mean, SEM) in groups 1 (▲), 2 (■) and 3 (●).

TABLE II. *Bupivacaine supplements (mean (SEM)).* P < *0.001 for the differences between group 3 and groups 1 and 2 by Logrank analysis*

	Time to first supplement (min)	Interval between supplements (min)
Group 1	135 (23.3)	163 (9.2)
Group 2	171 (22.7)	163 (8.9)
Group 3	99 (26.5)	106 (10.4)

arterial pressures of < 100 mm Hg were recorded. No patient required a vasoconstrictor and the differences were statistically insignificant. No patient developed a ventilatory frequency less than 10 b.p.m. at any time.

TABLE III. *Sedation scores (mean (SEM))*

Time	Group 1	Group 2	Group 3	*P*
20 min	1 (0.18)	0.68 (0.15)	0.08 (0.07)	< 0.01
40 min	0.95 (0.15)	0.84 (0.12)	0.08 (0.07)	< 0.001
60 min	0.75 (0.22)	0.67 (0.13)	0.22 (0.11)	
2 h	0.8 (0.18)	0.83 (0.19)	0.23 (0.12)	
4 h	0.71 (0.19)	1.2 (0.31)	0.7 (0.39)	

Eight patients in group 1 ($n = 18$), nine in group 2 ($n = 19$) and seven in group 3 ($n = 14$) developed nausea or vomiting. Using the chi-square test, no significant differences were found between the groups. Nine patients in group 1, 10 in group 2 and six in group 3 developed urinary retention. Again, the chi-square test showed no

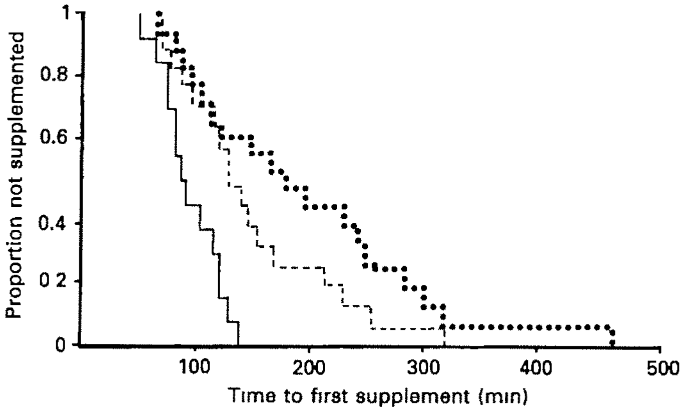

FIG. 2. Cumulative survival curve of time to first supplement of bupivacaine in groups 1 (——), 2 (●●●) and 3 (——).

difference between the groups. Nausea, vomiting and urinary retention increased with progress of labour.

Paraesthesiae were minimal in the opioid groups during the first 2 h, but increased as more bupivacaine supplements were given. However, 4 h after the initial injection, significantly fewer group 2 patients had paraesthesiae ($P = 0.001$).

Pruritus was absent in the bupivacaine group, 12 of group 1 and 14 of group 2 patients experienced this side effect ($P = 0.05$, $P = 0.005$ and $P = 0.01$ at 60 min, 2 and 4 h, respectively).

Motor block was initially less in the opioid groups, but increased as more bupivacaine was given. No statistical differences were obtained.

Apgar scores were generally satisfactory. However, one baby in group 1 had Apgar scores of 3 and 8 at 2 and 5 min, respectively. Another in group 3 had scores of 4 and 10 at the same times. Both had undergone delivery by forceps.

DISCUSSION

Pethidine was an early opioid to be given extradurally [4] and it was shown to be effective in labour to a varying degree. Its short duration of action led Perris and Malins to add adrenaline 1:200000 in a subsequent study [5] and this produced a longer duration of action. Other work [6] compared pethidine and saline with pethidine and adrenaline, and failed to detect any significant differences in either efficacy or duration of action. Husemeyer and colleagues [7] suggested that extradural pethidine compared favourably with i.m. pethidine because of greater plasma concentrations, rather than a specific spinal cord action. However, Vella and others [8] demonstrated that fentanyl has a potent extradural effect in labour, supporting earlier work [9] which showed distinct superiority of extradural over i.m. fentanyl for obstetric analgesia. Extradural pethidine [5], fentanyl [10], alfentanil [11] and morphine [12] appear to provide poor analgesia in the second stage. Analgesia during the first stage was found by Heytens to be good with alfentanil [11], but some neonates in this study were hypotonic.

Extradural morphine has been shown to be of variable efficacy in low doses [13–15] for obstetric analgesia, but Hughes and colleagues [12] obtained greater reliability with doses of 7.5 mg, although they suggested a local anaesthetic given extradurally would be more suitable for the second stage.

Later studies have used local anaesthetic–opioid mixtures in order to reduce the doses of both types of drug. Thus fentanyl–bupivacaine mixtures [16] in low concentration extradural infusions produced good analgesia with reduced motor block, whilst sufentanil with bupivacaine and adrenaline decreased onset time whilst increasing quality and duration of analgesia compared with bupivacaine alone [17].

In this study we have compared extradural diamorphine with bupivacaine. We have also examined the effect of adrenaline 1:200000 on the efficacy and duration of action of diamorphine. In these respects, our study differed considerably from that of McGrady, Brownhill and Davis [1] who showed that a combination of diamorphine and bupivacaine by infusion was highly effective.

We observed that diamorphine 5 mg and 0.375% bupivacaine 8 ml were comparable in terms of analgesia. Both had a rapid onset time and most patients obtained satisfactory pain scores after 20 min. Extradural diamorphine enters the spinal cord rapidly, as it is lipophilic. It may pass through the dura, through the arachnoid granulations or via the posterior radicular arteries to the cord [18]. Diamorphine thus has a more rapid and predictable onset time than morphine which, although it is a smaller molecule and crosses the dura faster [19], is more hydrophilic.

Adrenaline reduces the vascular uptake of diamorphine from tissues, and this may account for the superior analgesia in group 2 from 60 min to the end of the study.

Despite the recommendations of *Martindale: the Extra Pharmacopoeia* [20], diamorphine was dissolved in saline to improve the tonicity of our solutions. Studies by Hain and Kirk [21] have suggested that this concentration (0.0625%) would be unlikely to precipitate even 24 h after constitution. In our study, solutions were used immediately after preparation and no precipitates were observed.

Sedation was greater in both opioid groups. It is interesting that peak sedation scores occurred later in group 2 (the adrenaline group) than in group 1. There was no case of oversedation and neonatal Apgar scores did not differ between groups. In addition, respiratory depression was not observed. Patients were monitored throughout labour and post partum observations did not reveal a ventilatory frequency less than 10 b.p.m. However, ventilatory frequency may not be a satisfactory index of hypoventilation [22].

In conclusion, we have observed that extradural diamorphine produced comparable analgesia of longer duration than bupivacaine in the doses used. The addition of adrenaline improved longer term analgesia and duration of action with fewer paraesthesiae and reduced requirements for bupivacaine supplements.

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PRIMING OF PANCURONIUM WITH MAGNESIUM

M. F. M. JAMES, P. A. SCHENK AND B. W. VAN DER VEEN

SUMMARY

Magnesium inhibits the release of acetylcholine from the motor nerve terminal and thus potentiates the action of the non-depolarizing neuromuscular blocking drugs. We have examined the possibility that this effect might enhance the speed of onset of non-depolarizing block with pancuronium. Following the administration of pancuronium 100 μg kg^{-1}, 95% depression of thumb twitch occurred in 68.3 (SD 25.9) s in magnesium-pretreated subjects and in 73.7 (19.5) s in a group given a priming dose (10 μg kg^{-1}) of pancuronium. Tracheal intubation was performed after 97.8 (22.5) s in the magnesium group and in 121.0 (37.5) s in the control group (ns). It is concluded that pretreatment with magnesium does not usefully increase the speed of onset of action of pancuronium.

KEY WORDS

Neuromuscular relaxants. pancuronium. Neuromuscular transmission · magnesium

Suxamethonium has remained the agent of choice for rapid sequence tracheal intubation techniques for emergency anaesthesia, primarily because of its extremely rapid onset of action and the profound nature of the neuromuscular block produced. Unfortunately, the well-known adverse reactions to this drug and the less common idiosyncratic responses are major disadvantages [1]. Non-depolarizing neuromuscular blockers (NDNMB) are devoid of many of the side effects of suxamethonium. However, despite intensive research, the development of an NDNMB capable of producing profound neuromuscular block with a speed of onset of action comparable to that achieved with suxamethonium has remained elusive. Investigation into this problem concentrated on the modification of administration schedules of established NDNMB, for example: supra-normal bolus doses, the priming principle and the use of combinations of two different NDNMB (purportedly with varying activity at different, specific receptor sites). None of these manoeuvres seriously challenges the role of suxamethonium for rapid sequence tracheal intubation [2].

The effect of NDNMB at the motor end-plate is potentiated by magnesium ions, which interfere with release of acetylcholine from the presynaptic terminal [3]. Conceivably, the reduced release of acetylcholine which magnesium produces, as opposed to the reduced mobilization produced by the NDNMB [4], could result in accelerated onset of paralysis. It is well known that the action of NDNMB is potentiated by magnesium in both animals and man [1], but the influence of the ion on the onset of action of NDNMB has not been studied.

This study compared the effect of magnesium sulphate ($MgSO_4$) pretreatment on the rate of onset of neuromuscular block produced by an intubating dose of NDNMB with a technique using the priming principle.

METHODS AND RESULTS

The study was approved by the Human Experimentation Ethics Committee of the Medical School, University of the Witwatersrand.

We studied patients (ASA I or II) of both sexes, aged 18–50 yr, undergoing elective surgery requiring tracheal intubation. Subjects meeting the inclusion criteria for the study were asked to give informed consent and were allocated randomly to one of two study groups (A and B) with 10 subjects in each group. Exclusion criteria included absence of informed consent, significant inter-

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TABLE I. *Cardiovascular responses in the two groups (mean* (SD)). *SAP, DAP = Systolic and diastolic arterial pressures; HR = heart rate*

	Group A (Magnesium)			Group B (Control)		
	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)	HR (beat min^{-1})
Baseline	141.9	90.0	74.0	140.8	78.7	77.0
	(20 0)	(16.2)	(16.7)	(19.6)	(10.0)	(13.3)
Induction	118 5	77 0	100.6	115.6	61 4	86.7
	(22.5)	(25.2)	(29.2)	(21.8)	(17.7)	(14.2)
Agent	118.5	77.8	110 2	117.7	71 4	104 9
	(28 7)	(23.7)	(20.9)	(17.0)	(14.2)	(13 3)
Intubation	135.8	85.6	112.8	142.1	88.3	112.4
	(18 4)	(16.6)	(18 1)	(17.9)	(17 9)	(14.0)

current disease, pregnancy or possible pregnancy, medication which could affect neuromuscular function, history of previous adverse reactions whilst under general anaesthesia and known allergy to any of the drugs to be used in the study.

Premedication consisted of hydroxyzine 1 mg kg^{-1} i.m., 1 h before induction of anaesthesia. All patients underwent preoxygenation for not less than 3 min. Three minutes before induction, group B subjects were given pancuronium 10 μg kg^{-1} i.v., whilst group A subjects received an equivalent volume saline. Anaesthesia was induced with propofol 2–3 mg kg^{-1} given over 30 s to loss of the eyelash reflex. Anaesthesia was maintained with 50 % nitrous oxide in oxygen administered via a Mapleson A breathing system with supported ventilation as required, supplemented by an infusion of propofol 100 μg kg^{-1} min^{-1}. Subjects in group A then received a "pretreatment" of $MgSO_4$ 60 mg kg^{-1} (0.25 mmol kg^{-1}) i.v. over 1 min, and patients in group B received an equivalent volume of saline. One minute after completion of the pretreatment, both groups received an "intubating dose" of pancuronium bromide 100 μg kg^{-1} as a bolus.

Twitch height was monitored continuously after induction using a single, repetitive, supramaximal twitch stimulus applied to the ulnar nerve at 2-s intervals, and the force of contraction in the adductor pollicis muscle was recorded using a Myograph strain gauge transducer attached to the thumb in the normal manner with a continuous written record made on the Myotest chart recorder. The time from administration of the 100-μg kg^{-1} bolus of pancuronium to 5 % control twitch height was determined. At this time, direct laryngoscopy was performed by an investigator blind to the patient group, and intubating conditions were assessed on a five-point scale: 1 = no jaw relaxation, unable to insert laryngoscope; 2 = gross movement in response to laryngoscopy; 3 = marked movement of vocal cord on visualization; 4 = minimal cord movement; 5 = ideal intubating conditions, with no movement.

If the intubating conditions were scored at 3 or greater, tracheal intubation was performed. If the score was 2 or less, laryngoscopy was terminated and intubation reattempted after a further 30 s. The time from administration of the intubating dose of pancuronium to intubation was noted. Blood samples, taken before induction of anaesthesia, after induction, after intubation and at the end of the procedure were analysed for serum concentrations of magnesium by atomic absorption spectrophotometry.

The ECG was monitored continuously and arterial pressure measured at 1-min intervals using a Dynamap automated arterial pressure recording device.

Statistical analysis of the numerical data was performed using Student's *t* test, and Fisher's exact test was used for testing distributions. Significance was defined as $P < 0.05$. Results for numerical data are presented as mean (SD).

Following administration of $MgSO_4$ there was a small, non-significant reduction in twitch height, and the mean serum concentration of magnesium at the time of intubation in group A was 2.34 (0.63) mmol litre^{-1}. Serum concentration of magnesium before operation was in the normal range (0.8–1.1 mmol litre^{-1}) in both groups. The interval from induction to 95 % depression of twitch height was 68.3 (25.9) s in the magnesium group and 73.7 (19.5) s in the control group. Intubation was performed after 97.8 (22.5) s in the magnesium group and after 121.0 (37.5) s in the control group (ns). Six patients in the magnesium group coughed with intubation, compared with four in the control group. No patient in either group was judged to be ready for tracheal intubation, with our scoring system, in less than 75 s. Loss of thumb twitch did not appear to be a reliable guide to laryngeal or diaphragmatic paralysis, particularly in the magnesium group. At the end of the procedure, approximately 50 min after induction, neuromuscular block was antagonized easily in both groups and there was no evidence of prolongation of the effect of pancuronium in the magnesium group. At this time the serum concentration of magnesium in the magnesium group was 1.23 (0.07) mmol litre^{-1}. There were no significant differences in cardiovascular variables between the groups (table I).

COMMENT

This study has demonstrated that, whilst magnesium may have some effect on the speed of onset of NDNMB, it is unlikely to produce significant, clinically useful effects on onset time with pancuronium. The serum concentrations of magnesium obtained were considerably less than the 5 mmol litre^{-1} at which neuromuscular weakness occurs and the 10–12 mmol litre^{-1} at which serious cardiac problems are seen [5]. It is conceivable that greater concentrations of magnesium could have produced a different result, but at the risk of significant paralysis occurring before administration of the blocking drug. It might be argued that there was a trend towards shorter onset times in the magnesium group, and that a larger sample size might have produced a statistically significant result. However, even if a statistically significant result was obtained, the reduction in onset time would still not be sufficient to allow this technique to be advocated for rapid sequence tracheal intubation, although it could be argued that the technique was marginally superior to the priming principle. Even in hypertensive obstetric patients in which $MgSO_4$ has been used for control of convulsions, suxamethonium remains the neuromuscular blocking drug of choice for rapid sequence tracheal intubation. It is of interest that, although subjects were judged to be ready for intubation earlier in the magnesium group, slightly more of them coughed, suggesting that the diaphragm may be more resistant than the adductor pollicis to magnesium. This is similar to the effect described for the non-depolarizing neuromuscular blockers [6], and might suggest varying sensitivity according to muscle type.

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TENSION PNEUMOTHORAX AND PULSE OXIMETRY

R. S. LAISHLEY AND C. APS

SUMMARY

A case is described of spontaneous tension pneumothorax occurring during preparation for thoracic surgery. The earliest indication of this was unexplained haemoglobin desaturation as detected by pulse oximetry. This case report provides another example of the early warning potential of pulse oximetry.

KEY WORDS

Complications tension pneumothorax. Monitoring techniques. pulse oximetry.

The occurrence of pneumothorax is a rare complication during anaesthesia. Tiret and colleagues reported one case in 198 103 anaesthetics over a 4-yr period in 460 institutions. Similarly, Lunn and Mushin [2], in their 12-month survey of 1 147 362 operations, reported only one case. When it develops, tension pneumothorax results in haemoglobin desaturation, impaired ventricular filling and ultimately, cardiac arrest. The advent of pulse oximetry [3] has allowed early detection of haemoglobin desaturation and has been recommended as a desirable method of patient monitoring during anaesthesia [4]. We describe a case of unanticipated tension pneumothorax which occurred during thoracic anaesthesia, detected at an early stage with pulse oximetry.

CASE REPORT

A 63-yr-old, 46.7-kg man underwent right upper lobectomy for adenocarcinoma of the lung. Preoperative evaluation revealed him to be functionally healthy, but with recent weight loss. Mild emphysematous changes were noted on his chest x-ray.

He was premedicated with papaveretum 10 mg and hyoscine 0.2 mg i.m. ECG monitoring was commenced in the anaesthetic room. Anaesthesia was induced with thiopentone 350 mg, alfentanil 0.5 mg and pancuronium 6 mg. The patient's lungs were ventilated by mask with 1.0 % isoflurane in oxygen until tracheal intubation. A medium sized left endobronchial Robertshaw double-lumen tube was passed without difficulty, and both lungs isolated easily as indicated by auscultation and chest movement. Following this, a lumbar extradural catheter was inserted with the patient in the right lateral position for postoperative opioid analgesia. During extradural cannulation a Manley ventilator was used to provide bilateral lung ventilation and patient monitoring was performed by a separate anaesthetist using the ECG, palpation of the pulse and clinical assessment of chest movement and the patient's colour.

The patient was moved into the supine position in the anaesthetic room and transferred into the operating theatre, where he was turned into the left lateral position. Both lungs were ventilated (Servo B) with 60 % nitrous oxide and 0.5 % isoflurane in oxygen. Initial oxyhaemoglobin saturation noted by the pulse oximeter finger probe (Sp_{O_2}) was only 70 %. Misleadingly, the patient appeared pink and well perfused. Clinical examination showed breath sounds and movement were present equally over both lung fields. Simultaneously, the inspired oxygen was increased to 100 % and the ventilator circuit checked. Peak airway pressures were noted to be 18 cm H_2O. Sp_{O_2} continued to decrease rapidly to 57 %. At this time arterial pressure (indirect) and heart rate (ECG) remained unchanged at about 95 mm Hg systolic and 75 beat min^{-1}, respectively. However, the neck veins were noted to be distended. With a strong suspicion of pneumo-

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thorax, right lateral thoracotomy was expedited, resulting in a sudden rush of gas from the pleural cavity. Sp_{O_2} increased to 100%, arterial pressure to 160 mm Hg systolic and the neck vein distension resolved. The remaining course of the anaesthetic proceeded uneventfully, except for one further event: following deliberate isolated left lung ventilation for 45 min, the right middle and lower lobes could not be reinflated until the left endobronchial cuff was deflated.

DISCUSSION

This case report describes another example of the early detection of intraoperative misadventure by pulse oximetry. Since the clinical introduction of pulse oximetry [5, 6], many advantages have been reported for this method of monitoring [3, 7], including its role in cyanotic congenital heart disease [8] and detection of hypoxaemia secondary to pulmonary oedema [9]. Tension pneumothorax during anaesthesia is relatively rare [1, 2] and we report this case to illustrate both the value of pulse oximetry in monitoring the position of double-lumen endobronchial tubes and in detecting tension pneumothorax.

The potential for barotraumatic pneumothorax in this thoracic patient was not thought to be particularly high compared with some who present for such surgery. Later inspection of the slightly emphysematous lung, did not reveal any bullae. It was fortunate that the tension pneumothorax occurred on the operative side of the chest. The earliest and most important indication that some serious event had occurred was provided by the pulse oximeter. With the exception of jugular venous distension, no other physical signs assisted in making the diagnosis. Indeed, such signs were so misleading that, had pulse oximetry been omitted, it is likely that further deterioration may well have remained undetected until cardiac arrest. Clearly, frequent monitoring with clinical examination of colour, equality of breath sounds and chest movement, together with arterial pressures and heat rates that were appropriate to the type of anaesthetic administered, gave little indication of the severity of the developing deterioration in the patient's condition. This episode underlines the fact that cyanosis is not a reliable clinical sign of hypoxaemia, despite the presence of severe haemoglobin desaturation.

The majority of complications associated with double-lumen endobronchial tubes include airway trauma [10] and malposition. The commonest cause of malposition is the use of a tube that is inappropriately small [11]. This may have been a factor in our patient. It is well recognized that repeated repositioning of patients, as in ours, is likely to increase the chances of an endobronchial tube becoming misplaced. This emphasizes the need for monitoring with pulse oximetry to be undertaken before and during anaesthesia in addition to the standard clinical methods for confirming tube position during surgery. As the right lung could not be re-inflated until the left bronchial cuff was deflated, we surmise that, despite apparent evidence to the contrary, the position of the tube allowed for sufficient hyperinflation of the right lung to cause tension pneumothorax.

We concede that our failure to begin pulse oximetry monitoring before the anaesthetic room procedures was an omission that denied earlier detection of a developing hazard. Arterial desaturation is common during one-lung anaesthesia [12] and the use of pulse oximetry throughout thoracic anaesthesia is clearly indicated for this reason alone.

This report illustrates the warning potential of pulse oximetry in the detection of severe haemoglobin desaturation, supports its use as *mandatory* monitoring during thoracic surgery and emphasizes the necessity for such monitoring to be undertaken before induction and not merely during maintenance of anaesthesia.

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THE HUMPHREY ADE SYSTEM: EVALUATION IN PAEDIATRIC USE

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SUMMARY

The Humphrey ADE single lever parallel form breathing system was evaluated in 17 children whose lungs were ventilated mechanically, mean age 28 (range 9–58) months, weight 13.3 (8.3–18.0) kg and in 10 spontaneously breathing children, age 50.7 (18–99) months and weight 17.5 (10.9–24.3) kg. During controlled ventilation in the E mode, the ADE behaved in a manner similar to the Jackson–Rees modification of Ayre's T*-piece with the fresh gas flows (FGF) set either according to weight or at a standard 3 litre* min^{-1}*. After 5 min hand ventilation in the A mode with FGF 3 litre* min^{-1} *the mean end-tidal partial pressure of carbon dioxide was 5.3 (*SD *0.8) kPa (range 4.1–7.7 kPa). Whilst breathing spontaneously in the A mode, no patient experienced rebreathing at FGF 3 litre* min^{-1}*; rebreathing started at 124 (31.6) ml* kg^{-1} min^{-1}*. The ADE circuit performed satisfactorily in all three modes. During controlled ventilation in the E mode, FGF should be adjusted according to the standard formulae recommended for the* T*-piece circuit. During hand ventilation in the A mode, an FGF greater than 3 litre* min^{-1} *should be used.*

KEY WORDS

Anaesthesia. paediatric Equipment: breathing systems, Humphrey ADE system.

The Humphrey ADE breathing system has been proposed as a universal anaesthetic system, incorporating Mapleson classification A, D and E modes and suitable for adult and paediatric usage [1]. These claims have been validated in adults. In children weighing less than 20 kg, Humphrey has claimed that the ADE system may be used for spontaneous ventilation in the A mode and controlled ventilation in the E mode, with a standard fresh gas flow (FGF) of 3 litre min^{-1} [2]. There has been no independent confirmation of these findings.

The purpose of this study was to assess the system in children during spontaneous and controlled ventilation. Although lesser FGF may be possible, we felt that the minimum safe limit for paediatric clinical practice was 3 litre min^{-1}.

We compared the Humphrey ADE system in E mode with the Jackson–Rees modification of the Ayre's T-piece (T-piece) during controlled ventilation, at an FGF either adjusted by weight or set at 3 litre min^{-1}. In the A mode, we tested the system at FGF 3 litre min^{-1} during spontaneous and hand ventilation. Finally, we assessed the margin of safety during spontaneous ventilation in the A mode by determining the FGF at which rebreathing occurred.

PATIENTS AND METHODS

Apparatus

The single lever parallel ADE system consists of a manifold which attaches to the FGF outlet of the anaesthetic machine. A single lever controls the mode of use by rotating a cylinder within the manifold. With the lever in the upright position, the ventilator is excluded, and the system consists of the reservoir bag in the inspiratory limb and the

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expiratory relief valve at the distal end of the expiratory limb (Mapleson A configuration). With the lever down, the ventilator is included and the reservoir bag and expiratory relief valve excluded (Mapleson E classification). The safety pressure limiting device is connected in both modes.

The version tested only allows two modes: A for spontaneous and E for controlled ventilation. Hand ventilation with the reservoir bag was possible only in the A mode.

We used 15-mm lightweight tubing (ISO standard size) which has a resistance to flow of 1 cm H_2O at 20 litre min^{-1} per 1.5-m length) [2] and a 500-ml reservoir bag. The MIE valve in the open position produces a pressure difference of 0.8 cm H_2O at FGF 15 litre min^{-1} and 1.4 cm H_2O at 30 litre min^{-1} (manufacturer's specification).

Monitoring

The paediatric cuvette (deadspace 2 ml) of an in-line capnometer (Hewlett–Packard 14360A) was connected directly to the tracheal tube. The capnometer was calibrated against a known standard before each study. The carbon dioxide waveform was recorded continuously on a Gould two-channel hot wire recorder. The accuracy of the flowmeters was confirmed against standard flowmeters (Fisher). The Infanta Wright Respirometer, used in the controlled ventilation group, is accurate to 5% at volumes between 15 and 200 ml [3] and was recalibrated by the manufacturer (Ferraris Medical Ltd).

Patients

The study was approved by the Ethics Committee of The Hospitals for Sick Children, London. We studied 17 children weighing up to 20 kg in the controlled ventilation group and a further 10 children up to 25 kg in the spontaneously breathing group. All were of ASA I or II status, undergoing peripheral urological or orthopaedic surgery (table I).

Procedure

Premedication in the controlled ventilation group, given 1 h before operation, comprised i.m. pethidine compound 0.08 ml kg^{-1} and atropine 0.025 mg kg^{-1} for children weighing less than 15 kg; papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} were given to those heavier than 15 kg. In the spontaneously breathing group, premedication comprised trimeprazine 4 mg kg^{-1} and atropine 0.05 mg kg^{-1} orally 2 h before operation.

In both groups, anaesthesia was induced with 50% cyclopropane in oxygen and changed to 66% nitrous oxide and 2–3% halothane in oxygen when the child was asleep.

A T-piece circuit was used in all patients, as the Humphrey ADE system is not antistatic and cannot be used with cyclopropane.

The trachea was intubated with an uncuffed Portex tube after administration of suxamethonium 1.5 mg kg^{-1}. A throat pack was used to ensure a tight seal. Caudal extradural block was performed with 0.25% bupivacaine 0.5–0.8 ml kg^{-1}. In all children, ECG and non-invasive arterial pressure (Dinamap, Applied Medical Research) were monitored continuously.

Controlled ventilation group. Anaesthesia was maintained with 67% nitrous oxide and 0.5% halothane in oxygen. Neuromuscular block was produced with tubocurarine and monitored with a peripheral nerve stimulator (Bard Medical). A Nuffield Penlon 200 modified with a Newton valve [4] was used for ventilation of the lungs.

The ADE in E mode was compared with the T-piece in the same patients undergoing ventilation at a constant minute volume (tidal volume of 10 ml kg^{-1} and ventilatory frequency 20 b.p.m.). Tidal volumes were set according to the Infanta Wright Respirometer. Two FGF were used: 3 litre min^{-1} irrespective of weight, or calculated according to the formula: FGF = 1000 + (200 × weight in kg) ml min^{-1}. This formula has been shown to achieve normocapnia in children undergoing ventilation with the T-piece [5]. An end-tidal carbon dioxide plateau was seen and recorded throughout.

The procedure adopted is described in the flowchart (fig. 1). Randomization was according to day of birth.

During hand ventilation in the A mode, the expiratory valve was adjusted to allow manual ventilation. During this time the operator could not see the values for end-tidal partial pressure of carbon dioxide (PE'_{CO_2}) which was monitored by a second anaesthetist, and obtained from the tracings at the completion of the study.

Spontaneously breathing group. Anaesthesia was

TABLE I. *Patient characteristics in the controlled and spontaneous ventilation groups (mean (range))*

	Controlled	Spontaneous
Age (months)	28.4 (9–58)	50.7 (18–99)
Weight (kg)	13.3 (8.3–18 0)	17.5 (10.9–24 3)
Total (M.F)	17 (15:2)	10 (7:3)

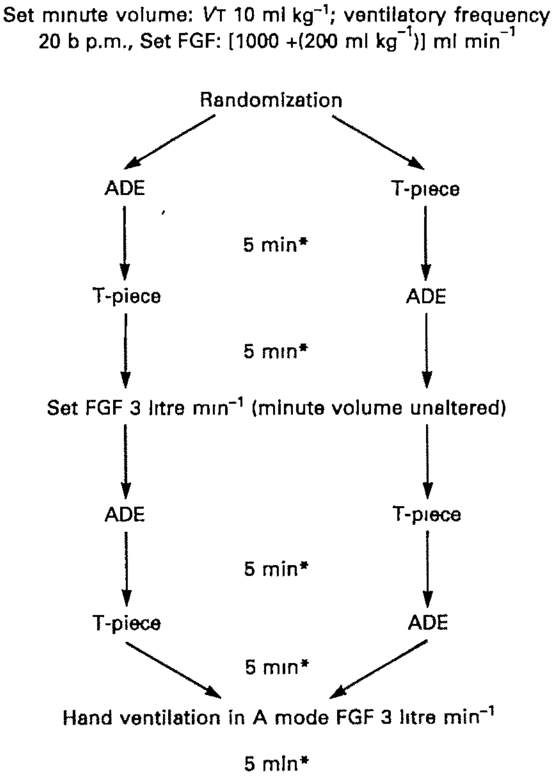
Set minute volume: VT 10 ml kg⁻¹; ventilatory frequency 20 b p.m., Set FGF: [1000 +(200 ml kg⁻¹)] ml min⁻¹
Randomization
ADE
T-piece
5 min*
T-piece
ADE
5 min*
Set FGF 3 litre min⁻¹ (minute volume unaltered)
ADE
T-piece
5 min*
T-piece
ADE
5 min*
Hand ventilation in A mode FGF 3 litre min⁻¹
5 min*

FIG. 1. Flow chart of events in the controlled ventilation group. *Measurement after 5 min.

maintained with 67% nitrous oxide and 1–2% halothane in oxygen with a total FGF of 6 litre min^{-1}. Fifteen minutes after the start of surgery and with PE'_{CO_2} stable for at least 5 min, FGF was reduced to 3 litre min^{-1}. After a further 5 min FGF was reduced by 200 ml every 2 min to 2 litre min^{-1} and thereafter by 100 ml every 2 min until rebreathing occurred according to both the following criteria: an increase in PE'_{CO_2} of 0.25% [6]; and a persistent increase in inspired carbon dioxide partial pressure (PI_{CO_2}) of 0.13 kPa (all of the inspiratory trace above the baseline and present for at least three consecutive breaths). FGF was then increased to 3 litre min^{-1} to note the effect on PI_{CO_2}.

Statistics

Mean values and SD were calculated. PE'_{CO_2} differences were evaluated using paired *t* tests. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Controlled ventilation group

Cardiovascular stability was present throughout. The two circuits behaved almost identically (tables II, III).

PE'_{CO_2} was significantly less with both circuits when fresh gas flows were adjusted according to the patient's weight. This is not surprising, as the weight-related fresh gas flows were generally greater than 3 litre min^{-1} (mean 4.28 (range 3.4–5.0) litre min^{-1}).

The greatest mean PE'_{CO_2} and widest range were in the group undergoing ventilation by hand in the A mode.

Spontaneously breathing group

Cardiovascular stability was present during the study.

PI_{CO_2} was continuously zero and the character of the carbon dioxide waveform and PE'_{CO_2} were identical with the FGF at 6 and 3 litre min^{-1}. PE'_{CO_2} increased at a mean FGF of 2.05 (SD 0.04) litre min^{-1}, equivalent to 124 ml kg^{-1} min^{-1}. A further reduction in FGF to 1.87 (0.34) litre min^{-1} or 112 ml kg^{-1} resulted in an increase in PI_{CO_2}.

Returning FGF to 3 litre min^{-1} restored PI_{CO_2} to zero within four to eight breaths.

There was no correlation between the FGF at which rebreathing occurred and either weight or age.

TABLE II. *End-tidal partial pressure of carbon dioxide (PE'_{CO_2}), comparing the ADE system with the T-piece at two different FGF; and the ADE in hand ventilation at 3 litre min^{-1}*

	PE'_{CO_2} (kPa)		
	Mean	SD	Range
ADE (FGF by weight)	4.8	0.6	3.9–5.5
T-piece (FGF by weight)	4.9	0.6	4.0–5.5
ADE (FGF 3 litre min^{-1})	5.0	0.6	4.3–6.3
T-piece (FGF 3 litre min^{-1})	5.1	0.7	4.1–6.1
ADE (hand, FGF 3 litre min^{-1})	5.3	0.8	4.1–7.7

TABLE III. *Means of the differences (95% confidence intervals) in* PE'_{CO_2} *values between the circuits at the same FGF, and within the two circuits at the two different FGF.* **$P < 0.01$; ***$P < 0.001$

Mode	Difference in PE'_{CO_2} (kPa)
ADE–T-piece (FGF 3 litre min^{-1})	0.01 (−0.10 to 0.12)
ADE–T-piece (FGF by weight)	−0.07 (−0.17 to 0.04)
ADE(E)–ADE(A) (FGF 3 litre min^{-1})	−0.31 (−0.71 to 0.08)
ADE (FGF 3 litre min^{-1})–ADE (FGF by weight)	−0.52 (−0.73 to −0.31)***
T-piece (FGF 3 litre min^{-1})–T-piece (FGF by weight)	−0.44 (−0.72 to −0.16)**

DISCUSSION

Humphrey has shown, in healthy adults during spontaneous ventilation in the A mode, that the single lever Humphrey ADE system in both coaxial and parallel forms was as efficient as the original two-lever ADE system and more efficient than the Magill or Bain systems. In controlled ventilation it was as efficient as the Bain system [7, 8]. He has suggested also that, in children weighing less than 20 kg, a standard fresh gas flow of 3 litre min^{-1} may be used for both spontaneous ventilation in A mode and controlled ventilation in E mode [2].

In our study we found that the ADE circuit in E mode behaved in a fashion almost identical to that of the T-piece. PE'_{CO_2} values were significantly less in both circuits with the FGF adjusted according to weight and values greater than the normal range were found in both circuits only when the set FGF of 3 litre min^{-1} was used. This is consistent with previous studies of Mapleson E classification systems [5]. It should be noted, however, that PE'_{CO_2} is influenced also by tidal volume in this type of system, and lesser values may be achievable if tidal volumes of greater than 10 ml kg^{-1} are used [9].

With an FGF of 3 litre min^{-1}, the mean PE'_{CO_2} in the hand ventilated group in the A mode (5.3 kPa) was greater than that during controlled ventilation with either the ADE (4.8 kPa) or T-piece (4.9 kPa) (ns). Nevertheless, we note that the range for this group was 4.1–7.7 kPa. Bearing in mind that switching to hand ventilation often occurs at more critical or difficult moments, we feel that the upper range of PE'_{CO_2} recorded precludes the use of FGF 3 litre min^{-1} during hand ventilation in the A mode.

During spontaneous breathing in the A mode in 10 anaesthetized children (mean age 4.1 yr, weight 15.8 kg), Humphrey found that rebreathing occurred at a mean FGF of 1.95 litre min^{-1} (123 ml kg^{-1} min^{-1}). Rebreathing was taken as PI_{CO_2} 2 mm Hg (0.27 kPa). This is similar to our figures of 2.05 litre min^{-1} (124 ml kg^{-1} min^{-1}) for an increase in PE'_{CO_2} and 1.87 litre min^{-1} (112 ml kg^{-1} min^{-1}) for an increase in PI_{CO_2}.

Conway commented on the difficulty in recognizing the rebreathing point by monitoring PI_{CO_2}, as this may vary even during one inspiration [10]. Chan, Bruce and Soni found that criteria based on measurement of PE'_{CO_2} are more sensitive indicators of rebreathing than those based on PI_{CO_2} [11]. Therefore, we noted the FGF at which the PE'_{CO_2} increased by 0.25 % and at which PI_{CO_2} increased by 0.13 kPa. The former occurred at greater FGF than the latter, although the difference was small. Increasing the FGF to 3 litre min^{-1} from the rebreathing point caused the carbon dioxide trace to return to normal within four to eight breaths. We concluded, therefore, that no rebreathing occurred in any of the children up to 25 kg with FGF 3 litre min^{-1}.

The standard against which potential paediatric breathing systems are tested is the Jackson–Rees modification of the Ayre's T-piece [12]. The principal advantages of the T-piece are its simplicity, lightness and lack of valves and thus minimal resistance to breathing. Its disadvantages include inefficiency during spontaneous breathing (an FGF of two to three times minute ventilation is recommended), inconvenience for effective scavenging and relative difficulty with hand ventilation for the occasional user.

In contrast, the Humphrey ADE system is extremely efficient during spontaneous breathing in the A mode allowing an FGF of 3 litre min^{-1} to be used with a considerable margin of safety in children weighing less than 25 kg. This has clear advantages for economy and could result also in better humidification, as there may be some rebreathing of deadspace gases. Scavenging from the ADE system is simple, as expired gases are led back to the manifold. For the occasional paediatric anaesthetist, hand ventilation may prove to be more convenient, as the configuration is similar to that used in adult practice, with both the expiratory valve and the reservoir bag at the anaesthetic machine.

Potential disadvantages of the ADE system include its weight, complexity and the presence of an expiratory valve. The lightweight paediatric 15-mm tubing weighs only 90 g at the face and the lever can be moved to only two positions, corresponding to the two modes. The presence of an expiratory valve is generally thought to be undesirable in a paediatric breathing system, because the extra resistance may increase the work of breathing and there is the possibility of the valve jamming. In the ADE system, the MIE valve has a very low resistance (0.8 cm H_2O at 15 litre min^{-1}) and has little, if any, consequences on the work of breathing. Nevertheless, the possibility of the valve becoming partially blocked and increasing the work of breathing is a serious consideration, although the pressure relief valve incorporated in the manifold should prevent barotrauma.

In conclusion, the single lever Humphrey ADE breathing system with 15-mm paediatric tubing is suitable for use in paediatric practice. During controlled ventilation in the E mode it behaves in a manner similar to the T-piece. During spontaneous breathing in the A mode, the possibility of the expiratory valve sticking and potential consequences should be borne in mind, and during hand ventilation (only possible in the A mode) an FGF greater than 3 litre min^{-1} should be used.

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RESISTANCE OF HUMIDIFIERS, AND INSPIRATORY WORK IMPOSED BY A VENTILATOR–HUMIDIFIER CIRCUIT

T. E. OH, E. S. LIN AND S. BHATT

SUMMARY

The pressures and resistances of a bubble humidifier (Bennett Cascade) and a blow-by humidifier (Fisher and Paykel) were measured and computed at gas flow rates from 4.5 to 100 litre min^{-1}*. Pressures increased with flows, with the Bennett pressures being greater at all flows. The resistance of the Fisher–Paykel increased with flows, but remained less than that of the Bennett. An inverse resistance–flow relationship was seen with the Bennett up to a flow of 35 litre min*$^{-1}$*. The work of breathing through a Servo 900C ventilator–humidifier circuit was computed, using a lung model. Work was performed by the Servo 900C on the lung, especially with the Fisher–Paykel circuit. The Bennett circuit required considerably greater (3.7 times more) inspiratory work. Thus the Bennett Cascade humidifier may present an unacceptable inspiratory load during spontaneous breathing.*

KEY WORDS
Airway. resistance to breathing. Equipment· humidifiers

The need for airway humidification in long-term mechanical ventilation is unquestioned. Heated water reservoir humidifiers are used in ventilator circuits to provide water vapour with little or no aerosol. There are two basic types of heated humidifiers: *bubble* or *cascade*, and *pass-over* or *blow-by* [1]. In bubble humidifiers, gas is dispersed through heated water, whereas in blow-by humidifiers, gas passes over the water surface. The Bennett Cascade (Bennett Medical Equipment, U.S.A.) and the Fisher–Paykel humidifiers (Fisher and Paykel Medical, New Zealand) are the most commonly used heated bubble and blow-by heated humidifiers, respectively.

It is recognized that successful weaning from mechanical ventilation may be determined by the heavy inspiratory load of some breathing systems [2, 3], but there is little published literature on the contribution of humidifiers to the work of spontaneous breathing. This study was undertaken to compare the flow resistances of the Bennett Cascade and Fisher–Paykel humidifiers, and the inspiratory work of a ventilator circuit with each humidifier.

MATERIALS AND METHODS

The resistances of a Bennett Cascade humidifier and a Fisher–Paykel humidifier (MR 500) were studied under constant flow conditions. Both humidifiers were filled with water, but remained unheated. Wall source air was passed into the inlet hose of each humidifier via a RT-200 Calibration Analyzer (Timeter Instrument Corp., PA, U.S.A.). The gas flow rate was set successively at 4.5, 7, 10, 15 and 20 litre min^{-1}, and thereafter at 10-litre min^{-1} increments to a maximum of 100 litre min^{-1}. At each constant gas flow rate, pressures were measured at both the inlet and outlet, using a differential strain gauge pressure transducer (Motorola MPX 10DP). Resistive pressure at each flow rate was given by the pressure decrease. Three sets of pressure and flow measurements were recorded with each humidifier. With the Fisher–Paykel circuit, a new disposable water chamber was used for each set of measurements.

Work of breathing was studied using a Servo 900C ventilator (Siemens Elema, Sweden). The Servo 900C was set to cater for spontaneous breathing (continuous positive airway pressure

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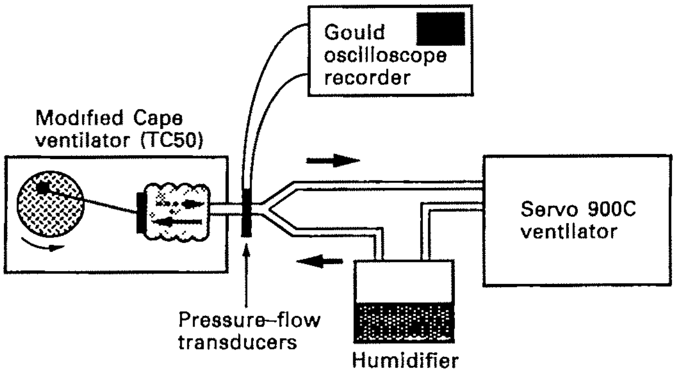
Gould oscilloscope recorder
Modified Cape ventilator (TC50)
Servo 900C ventilator
Pressure–flow transducers
Humidifier

FIG. 1. Schematic diagram of model lung to simulate spontaneous breathing. The Servo 900C ventilator was set to the "CPAP" mode.

(CPAP) mode), with a triggering sensitivity marginally greater than 0 cm H_2O. Spontaneous ventilation was simulated using a modified Cape TC 50 ventilator (Cape Engineering, England), adjusted to simulate a tidal volume of 600 ml at a rate of 15 b.p.m. and with a peak inspiratory flow of about 45 litre min^{-1} (fig. 1). Airway pressures and flows were measured at the patient airway, using a strain gauge pressure transducer (Motorola MPX 10DP) and a platinum hot wire flow transducer (Ohmeda SE 302T). The pressure and flow transducers were calibrated with the RT-200 Calibration Analyzer. Simultaneous pressure and flow signals were digitized at a rate of 200 s^{-1} and recorded and displayed on an oscilloscope (Gould DSO 1604).

Work of breathing imposed by the whole breathing system was derived from the pressure–flow values. The product of pressure (P) and flow ($\dot{V}$) gives instantaneous power ($\dot{W}$) at that moment. Power over a defined time interval (T_0–T_T) is given by integration of $P.\dot{V}$ over that time. Work during that time interval is then given by

$$W = \int_{T_0}^{T_T} \dot{W}.\mathrm{d}t$$

This method of determining work done has been described previously [2, 4]. Inspired tidal volume (VT) was derived from integration of flow during the inspiratory phase TI. Work of breathing was converted to J/litre of ventilation.

Data were analysed by linear and polynomial regression and a comparison between the two humidifiers was made using analysis of variance; $P < 0.01$ was considered significant.

RESULTS

The three sets of pressure recordings with each humidifier were nearly identical. The coefficient of variation for the pressure recordings ranged from 0.1 to 2.8 % except at the smallest flows. At a flow rate of 4.5 litre min^{-1}, the coefficient of variation was 5.9 % for the Fisher–Paykel and 8.7 % for the Bennett Cascade. Resistive pressures increased with greater flows (fig. 2, table I). The pressure:flow curves were fitted with a second order polynomial with $r = 0.999$ for the Bennett

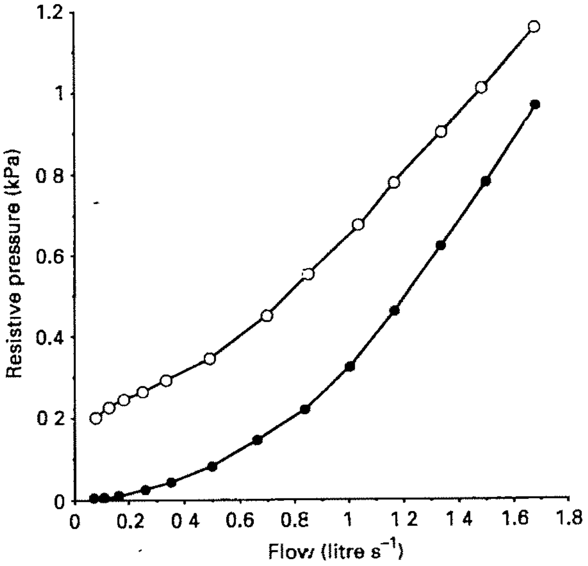

FIG. 2. Pressure–flow curves of Bennett Cascade humidifier (○) and Fisher–Paykel humidifier (●). Pressures of the Bennett are greater at all gas flows.

TABLE I. *Pressures and resistances of Fisher–Paykel (F–P) and Bennett Cascade (Bennett) humidifiers related to gas flow rates*

Mean flow (litre min^{-1})		Mean pressure (kPa)		Mean resistance (kPa $litre^{-1}$ s)	
F–P	Bennett	F–P	Bennett	F–P	Bennett
4.5	4.5	0.003	0.200	0.045	2.665
7.0	8.0	0.006	0.231	0.053	1.736
10.0	10.5	0.011	0.242	0.063	1.383
15.3	15.1	0.025	0.263	0.097	1.045
20.8	20.1	0.042	0.295	0.120	0.884
30.0	29.8	0.084	0.347	0.168	0.699
40.0	41.9	0.147	0.452	0.221	0.640
50.5	51.4	0.221	0.558	0.263	0.650
60.6	62.5	0.326	0.673	0.322	0.645
70.2	70.5	0.463	0.779	0.395	0.663
80.5	80.9	0.621	0.905	0 463	0.670
90.5	90.1	0.779	1.010	0.516	0.673
100.7	100.5	0.968	1.157	0.571	0.673

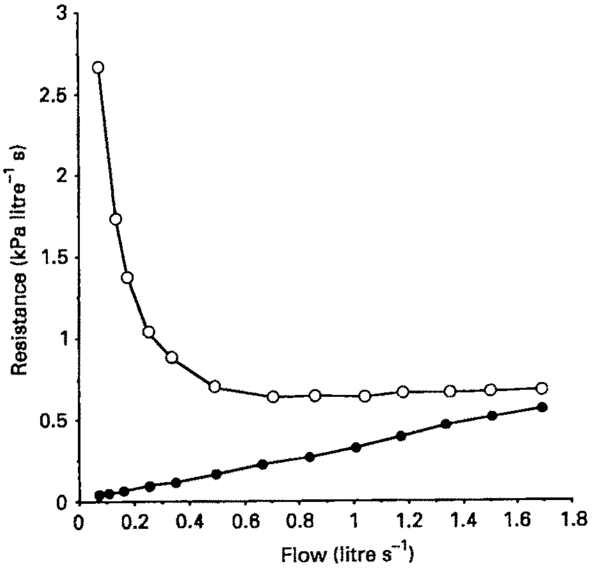

FIG. 3. Resistance–flow curves of Bennett Cascade humidifier (○) and Fisher–Paykel humidifier (●). The Bennett has an inverse relationship for flows up to 35 litre min^{-1}.

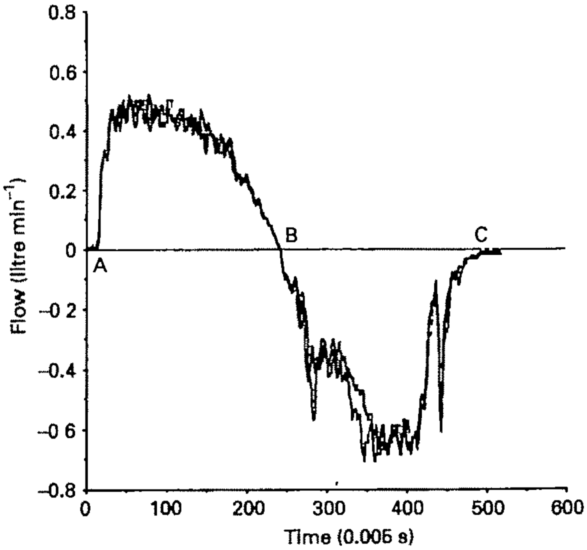

FIG. 4. Flow curves of a simulated spontaneous breath from a Servo 900C ventilator with a Fisher–Paykel (dotted line) and a Bennett Cascade (solid line) humidifier in circuit. A–B = Expiratory phase; expiratory flows are identical. B–C = Inspiratory phase shown with a negative polarity; peak inspiratory flow was set at 0.75 litre s^{-1} (45 litre min^{-1}).

Cascade and $r = 1.000$ for the Fisher–Paykel. Resistive pressure at each flow rate with the Bennett Cascade was always greater compared with the Fisher–Paykel ($P < 0.001$).

Calculated resistances (table I) were plotted against flow rate (fig. 3). The Bennett Cascade's resistance was high initially, but decreased sharply with increasing flows up to 35 litre min^{-1}. Thereafter, it remained relatively constant at a mean of 0.66 kPa $litre^{-1}$ s. With the Fisher–Paykel, resistance showed a small linear increase with increasing flow ($r = 0.998$) but was always less than the Bennett's resistance ($P < 0.001$). Resistances at 45 litre min^{-1} were 0.22 kPa $litre^{-1}$ s for the Fisher–Paykel, and 0.64 kPa $litre^{-1}$ s for the Bennett Cascade.

In the work of breathing experiments, the lung model produced identical curves in each ventilatory cycle for both flow and pressure. The flow curves of the Servo 900C system with each humidifier are shown in figure 4. Simulated inspiration was accorded a negative polarity for easier visualization. The expiratory flow curves were identical and the inspiratory curves almost identical for the two humidifiers. However, corresponding inspiratory pressure curves (fig. 5) were different. The Bennett Cascade generated larger negative inspiratory pressures (maximum of −0.43 kPa) than the Fisher–Paykel (maximum of −0.24 kPa). Computed inspired V_T was 680 ml.

Power curves for both humidifiers are shown in figure 6. Positive values denote the power required to overcome the resistance of the system, whereas negative values are the power inherent in the

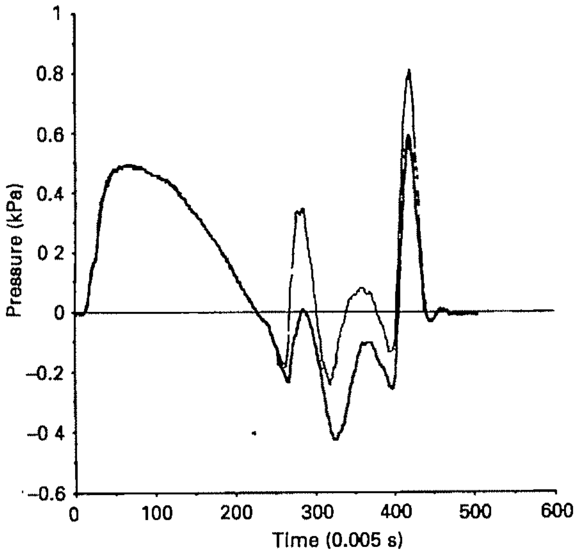

FIG. 5. Pressure curves of a simulated spontaneous breath from a Servo 900C ventilator with a Fisher–Paykel (dotted line) and a Bennett Cascade (solid line) humidifier in circuit. Expiratory curves are identical and shown here to precede inspiration. Inspiratory curves show extremely rapid pressure changes. The Bennett Cascade generated greater negative pressures.

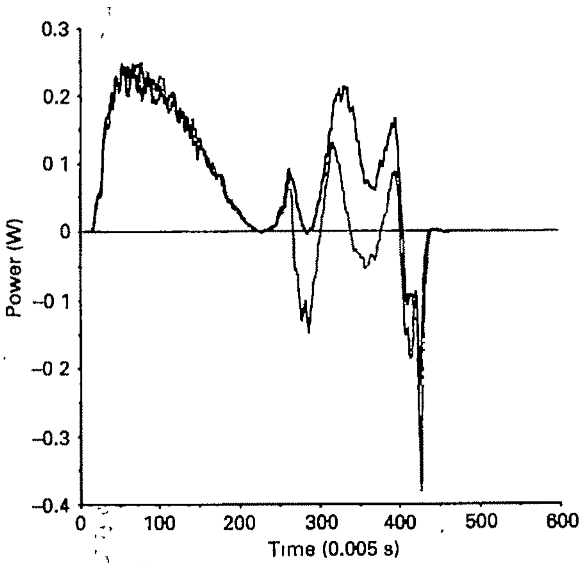

FIG. 6. Computed power curves of a simulated spontaneous breath from a Servo 900C ventilator with a Fisher and Paykel (dotted line) and a Bennett Cascade (solid line) humidifier in circuit. Expiration is represented here to precede inspiration. Negative power values denote work done on the lung by the breathing system. The Bennett Cascade required greater power during inspiration.

TABLE II. *Work done (J litre^{-1}) during a simulated spontaneous breath using a Servo 900C ventilator system with the specified humidifier in-line*

Humidifier	Inspiratory phase	Expiratory phase	Total
Fisher–Paykel	−0.032	0.140	0.108
Bennett Cascade	0.087	0.137	0.224

system because of an assist effect of the ventilator (see below). Work done during a simulated spontaneous breath is given in table II. Inspiratory work (*W*I) with a Bennett Cascade in the circuit was 0.087 J litre^{-1}; with the Fisher–Paykel circuit it was −0.032 J litre^{-1}.

DISCUSSION

Previous studies have reported values for work of breathing in ventilators and tracheal tubes [2, 3, 5–15], but reports on humidifiers are few. This is somewhat surprising, as humidifiers were designed originally for mechanical and assisted ventilation, and not specifically for spontaneous breathing. Dennison and co-workers [5] studied the resistances of eight circuits, including two with a Bennett Cascade humidifier, but tracheal tubes were attached. Mecklenburg and colleagues [2] reported on the resistance and work of breathing of the Kontron ventilator and its humidifier, a bubble device. Our present study compared the Bennett Cascade with the Fisher–Paykel, a blow-by humidifier.

With both humidifiers, increasing resistive pressures were produced by increasing flows. Greater resistive pressures were seen with the Bennett Cascade as expected, as it requires gas to be drawn through water. The curvilinear pressure–flow curve obtained with the Bennett Cascade was similar to that reported by Dennison and co-workers for a Bennett Cascade circuit with a 9-mm tracheal tube [5].

When resistances were computed, the Bennett Cascade demonstrated an inverse relationship between resistance and flow for flow rates less than 35 litre min^{-1} (fig. 3). This phenomenon was reported also by Dennison and co-workers [5] and may be caused by the complex passage of gas through the Bennett Cascade. Gas is drawn through water in its chamber and then through a grid, creating froth [1] which decreases resistance to gas flow. Low gas flows may produce proportionately less froth and thus meet with greater resistance. As a corollary, if sufficient froth is produced by adequate flows, resistance remains relatively constant. This resistance was demonstrated in our study to be 0.66 kPa litre^{-1} s with flows greater than 35 litre min^{-1} (fig. 3).

The Fisher–Paykel humidifier, on the other hand, has gas passing over the water surface [1]. Resistance would be expected to be less than that of bubble humidifiers. In addition, it incorporates filter paper wicks to increase water surface area effectively. Thus increased flow rates are likely to increase turbulence within the unit, giving rise to increases in resistance. The resistance increases were small in this study.

There are no specifications for a maximum resistance to flow applicable to humidifiers, as far as we know. Nunn recommended an upper limit of about 0.6 kPa litre^{-1} s at a flow rate of 30 litre min^{-1} for a breathing system [16]. The resistance of the Fisher–Paykel alone at the same flow was 0.17 kPa litre^{-1} s (with a maximum of 0.57 kPa litre^{-1} s at 100 litre min^{-1}). However, the resistance of the Bennett Cascade was considerably greater than the recommended upper limit at low flows, and approximated that limit with flows greater than 30 litre min^{-1}. Consequently, the resistance of a ventilator circuit with a Bennett Cascade humidifier would be considerably greater than 0.6 kPa litre^{-1} s.

The humidifiers were studied also in a simulated clinical setting using a popular modern intensive care ventilator, the Servo 900C. A simulated peak inspiratory flow of 45 litre min^{-1} was chosen, which approximates to those of stable weaning patients [5, 11]. However, our lung model was not able to produce physiological expiratory flows. Hence computed work done on expiration might be expected to be artificially high. Nevertheless, this did not affect the experiment, as differences in pressure and work of breathing were produced in the inspiratory phase. Our study was not designed to examine natural work against the patient's own compliance and resistance.

The work of breathing for a single breath is expressed appropriately in terms of joules or J/litre of inspiration. Thus the Servo 900C–Bennett Cascade system demanded 3.7 times more work than the Fisher–Paykel system for an inspiratory breath with a peak flow of 45 litre min^{-1}. Nevertheless, the Bennett Cascade's inspiratory work (0.087 J litre^{-1}) is much less than the 0.544 J litre^{-1} (0.272 J for 500 ml V_T) reported for the Kontron ventilator with its humidifier [2].

"Normal" work in breathing directly from atmosphere at rest is about 0.5 J litre^{-1} [8, 15]. The Servo 900C–Bennett Cascade system thus demanded 17.4% additional work. On the other hand, the Servo 900C–Fisher–Paykel system performed work on the lung. This "reduced work" characteristic of the Servo 900C was reported also by bench [8, 10, 11] and clinical [9] studies on the work of breathing imposed by demand valves of different ventilators. Comparison with our study is difficult, as the circuits in these studies either excluded in-line humidifiers [9] or included tracheal tubes [8, 11] or use of CPAP [10]. The experimental model of Katz, Kraemer and Gjerde included unspecified in-line humidifiers and found that the Servo 900C reduced work by −0.025 to −0.035 J litre^{-1} at peak flows of 20–60 litre min^{-1} [8]. A reduced work of −0.020 J litre^{-1} at a flow of 20 litre min^{-1} was reported by Bersten and colleagues [11] with a Fisher–Paykel humidifier and a 7-mm tracheal tube. Our value of −0.032 J litre^{-1} without a tracheal tube, at a flow of 45 litre min^{-1}, is consistent with the values reported above.

The larger negative inspiratory pressures seen with the Servo 900C–Bennett Cascade system confirmed the Bennett's greater resistance. For both humidifiers, an assist effect from the ventilator during the inspiratory phase was obvious. The Servo 900C directs gas into the circuit during inspiration from a pressurized concertina reservoir bag [1, 17]. Hence inspiratory flow can exceed demand, as represented by the increase in airway pressure to greater than that of end-expiration [8] (fig. 5). This would explain the "reduced work" effect of the Servo 900C ventilator.

The pressure flutter during inspiration (fig. 5) can be explained by the inspiratory demand valve of the Servo 900C. This scissors valve is activated by a servo-controlled, rapid cycling stepper motor [17]. A delay of about 0.15 s follows the start of a patient breath before the occluded valve opens [18]. As gas rapidly enters the circuit, a positive pressure is recorded. The gas delivery, patient inspiratory effort, circuit resistance and servo valve result in an inspiratory pressure flutter. This flutter can be significant if the patient's inspiratory flow demands are not met.

Excessive circuit resistance can cause respiratory muscle fatigue and prolong weaning from mechanical ventilation. The humidifier and the ventilator's inspiratory demand valve are the major contributors to the inspiratory resistance of a breathing system. Higher circuit resistances require greater negative intrapulmonary pressures to initiate each spontaneous breath, thus increasing the work of breathing. The peak inspiratory flows of weaning patients are usually about 40–50 litre min^{-1}, but greater flows may be required under stress [5]. If flow from the breathing system is insufficient to meet inspiratory demands, the resistive load on the patient is further increased. This is especially pertinent to the Bennett Cascade humidifier.

In conclusion, the resistance and inspiratory work imposed by the blow-by Fisher–Paykel humidifier is acceptable over the relevant range of patient inspiratory flows. However, the Bennett Cascade humidifier requires much more work for a spontaneous breath, and even by itself, has considerably greater resistances at the same flow rates. These findings confirm our clinical observation that patients are difficult to wean with the Bennett Cascade humidifier. Thus the Bennett Cascade humidifier should not be used for weaning, unless the ventilation mode or gas flow is able to reduce the work of breathing, such as with a Servo 900C. Indeed, the use of bubble humidifiers for spontaneous breathing is questioned.

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ANAESTHETIC EQUIPMENT FOR A DEVELOPING COUNTRY

J. PEDERSEN AND M. NYROP

SUMMARY

A development aid project to Malawi is described. This involved the development of a suitable anaesthetic machine for use in underdeveloped countries and the selection of a suitable oxygen concentrator to provide it with air and oxygen. All government hospitals were provided with anaesthetic equipment and personnel were trained to keep it regularly serviced. Follow up testing of reliability was undertaken. The cost benefit to the country amounted to £234084 (sterling) per year. This is the first instance of widespread use of standardized anaesthetic equipment which includes oxygen concentrators.

KEY WORDS

Equipment: anaesthetic machine, oxygen concentrator, vaporizers.

As one of the low income countries in Africa, Malawi shares many anaesthetic problems with other developing countries, including transport difficulties and insufficient staff training. One of the authors (J.P.) worked in Malawi from April 1982 to June 1989, as project manager for Danida (Danish Industrial Development Agency). Upon arrival, he found that each hospital had different anaesthetic equipment, of varying makes and countries of origin. The only common characteristic was that they were all dependent on continuous gas flows. Some district hospitals also had an EMO vaporizer [1], but often it could not be used, either because the concentration control had jammed, or the thermocompensator valve had failed. All the anaesthetic equipment had been given to the Malawi Government as gifts from other governments or missions. Some newly donated anaesthetic machines were already obsolete when they arrived in the country, so spare parts would be unobtainable in the future.

The anaesthetic equipment had rarely if ever been serviced [2] during the previous 5–10 years. The reasons included lack of spare parts, lack of tools to repair equipment and insufficient technicians trained to service the equipment.

The Medical Technical Unit had a service centre–store house of 8 m^2. Five technicians, all trained abroad, had the responsibility of servicing all the medical equipment in the 23 Government hospitals throughout the country. When they ordered spare parts, it took 12–18 months from the day they identified the need to the time the spare parts arrived in the country.

The provision of oxygen for the different districts hospitals was another major problem. When a district hospital sent staff to collect oxygen cylinders from the only company supplying gas, they were frequently not allowed the necessary number of cylinders. Often, the hospital lacked transport to collect cylinders. Many district hospitals bought fewer cylinders than needed because of their limited budget (one 48-ft^3 (1.36 m^3) oxygen cylinder costs £3.73 (sterling)). The oxygen cylinders often leaked.

The anaesthetic staff at district hospitals had only undergone a 2–6 week training programme. When they were transferred from one district hospital to another, they had to start working with a different anaesthetic machine; this was especially difficult for those with limited theoretical knowledge. Visiting surgeons or gynaecologists frequently transferred more complicated patients back to a central hospital and many patients, who

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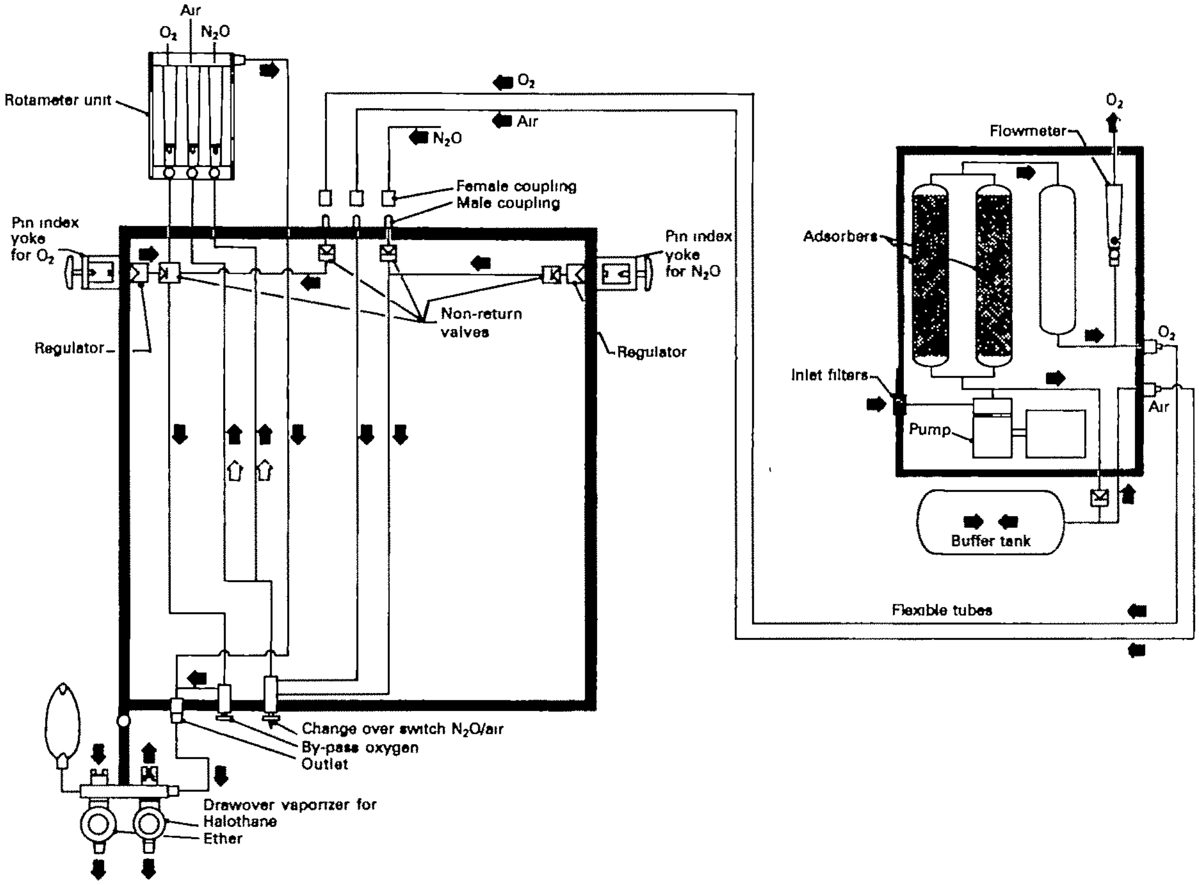

FIG. 1. Internal diagram of the oxygen concentrator connected to the Malawi anaesthetic apparatus with pipelines for oxygen and atmospheric air.

could have undergone surgery at a district hospital, were transferred also because of the lack of safe anaesthetic services at district level.

History of the Development Aid Project

Aware of the problems, one of the authors (J.P.) wrote a report to the Malawi Ministry of Health in September 1982 [personal correspondence with Ministry of Health, Malawi 15.9.82], and suggested the purchase of anaesthetic equipment which complied with International Standards Organisation (ISO) recommendations, combined with an oxygen concentrator [3].

The development of the Malawi anaesthetic equipment, specially designed for a developing country, was commenced in 1985 by the second author (M.N.) The aims in developing the new anaesthetic apparatus were ease of use, versatility and ease of servicing.

The design principles were that all units should be similar and incorporate the ISO standards, so that the units could be serviced anywhere in the country with the same procedure.

We tried to determine if an oxygen concentrator could deliver the necessary amount of oxygen and atmospheric air to a specially designed anaesthetic apparatus. After testing, it was decided that the DeVilbis oxygen concentrator model DeVo/44 (DeVilbis, Somerset, PA 15501-0635 U.S.A.) satisfied our requirements. Oxygen concentrators have been used for many years, and have been described in several articles [4–6], but not used on a large scale and in combination with an anaesthetic machine. In order to avoid fluctuation in oxygen flow, a buffer tank was incorporated in the system, at the outlet of the concentrator (fig. 1).

It is desirable to have atmospheric air available for use in the anaesthetic apparatus. Air for the anaesthetic gas system is taken, therefore, from

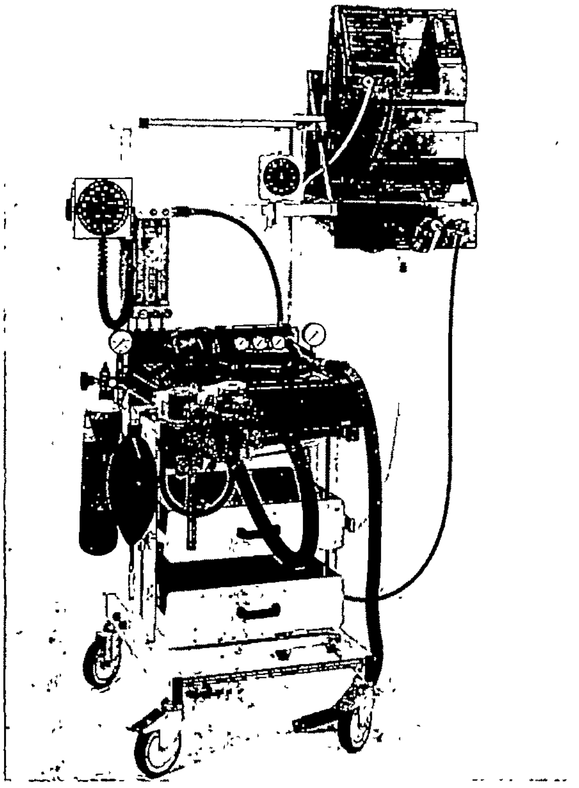

FIG. 2. Oxygen concentrator connected to the Malawi anaesthetic apparatus with pipelines for oxygen and atmospheric air.

the output line of the pump before it leads to the sieve beds. Both oxygen and atmospheric air are connected to quick release couplings mounted on the front panel. The pressure in the system before the outlet for oxygen and atmospheric air is approximately 180 kPa.

In the operating theatre, the oxygen concentrator may be placed in a wall bracket (fig. 2) mounted 1.5 m above the floor (safety height). High pressure flexible pipelines fitted with quick release connectors link the oxygen output from the concentrator to the socket fitted on the front plate of the wall bracket. The compressed atmospheric air from the concentrator is led via the built in non-return valve to the buffer tanks, and from there to the quick release connector on the front plate. This arrangement enables the concentrator to be disconnected and removed at short notice without using tools, should it be necessary to replace the concentrator or use it for other purposes.

It should be noted that the flowmeter on the concentrator may be used if the concentrator is used alone.

The Malawi Anaesthetic Trolley

The apparatus is based on the design of the traditional anaesthetic trolley. Pin index yokes are placed on the side panels, one for the oxygen cylinder on the left and one for a nitrous oxide cylinder on the right. Both take cylinders up to Size E (64 × 102 mm).

The yokes are connected to reducing valves, with a machine pressure of 300 kPa (3 bar), and thence to non-return valves. The rear panel of the trolley unit is equipped with non-interchangeable connections for flexible pipelines for oxygen, atmospheric air and nitrous oxide. The internal gas tubing of the unit has non-return valves at the connection points for the oxygen and nitrous oxide pipelines to prevent gas escape when using cylinders but not pipelines.

On the front plate of the apparatus, there is an oxygen flush valve for oxygen supply direct to the patient system, and a selector switch between nitrous oxide and atmospheric air. This prevents accidental hypoxia which would arise if nitrous oxide and atmospheric air were added simultaneously.

The flowmeter unit is equipped with three antistatic flowmeters. Those for oxygen and nitrous oxide are calibrated from 0.2 to 12 litre min^{-1}, while that for atmospheric air is calibrated from 0.2 to 15 litre min^{-1}.

The gases leave from the left side of the flowmeter bank and pass by flexible tubing to a swing console, which is mounted at the front on the left side, and fitted with two PAC drawover vaporizers (Cyprane, Ohmeda, New Devonshire House, Scott St West, Cheshire BD21 2NN, U.K.) for ether and halothane. The console is sited here as it is convenient for the breathing system in relation to the patient, and it is easy to use the vaporizers, as these may be placed close to the anaesthetist. The vaporizer console swings around an upright pole which keeps the vaporizers in a vertical position.

Gas enters the vaporizer on the left of the console close to the reservoir bag near a pressure limiting valve. If the input flow exceeds the patients's minute volume, excess gas escapes through this valve. This pressure limiting valve opens at 1 kPa and so it is not possible to use the reservoir bag for artificial ventilation and it also

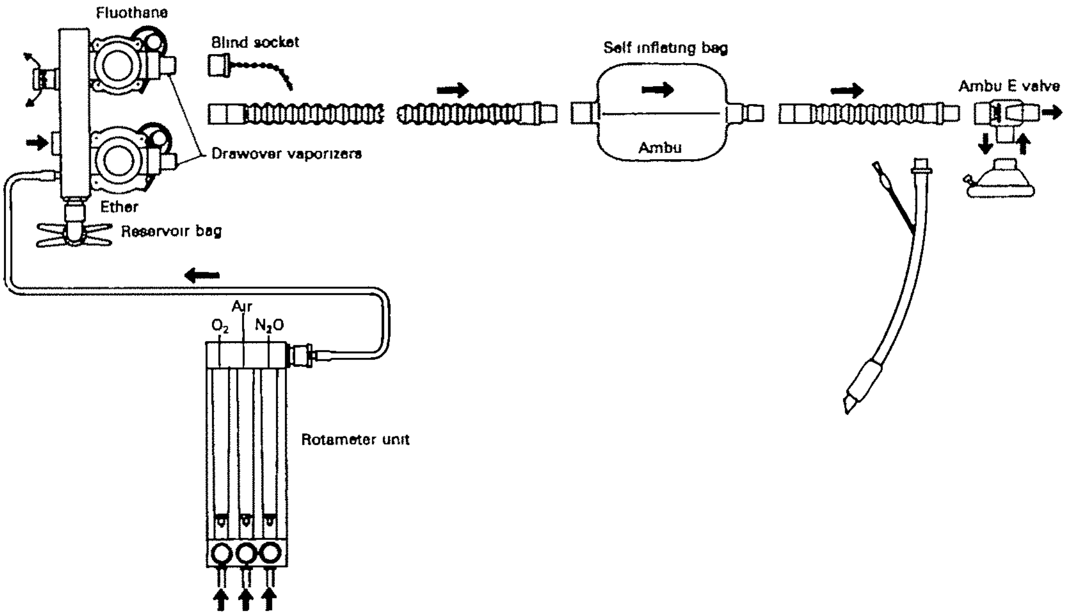

FIG. 3. Patient system connected to drawover vaporizer for halothane or ether. Expired gases are led to the floor through a corrugated tube fitted with a 30-mm male taper.

prevents production of a positive pressure at the inlet of the vaporizer which would cause a vapour concentration greater than that set. If the supply of fresh gases through the flowmeter is inadequate, the patient inspires room air through a low pressure valve which opens at 0.03 kPa.

If desired, the vaporizer console may be dismounted easily and attached to a wall rail system by two claws positioned at the rear. The ISO recommendation that it should not be possible to connect two vaporizers in series is followed in that it is only possible to attach the patient breathing system to one vaporizer at any time; a blank socket is available to seal off the vaporizer not in use. Ether and halothane vaporizers were chosen, as these two anaesthetic agents are most commonly available in district hospitals. A trichloroethylene vaporizer is not incorporated because medical production of this agent has been discontinued in many countries.

Patient system

The corrugated tubes are fitted with metal ISO 22-mm connectors (gas flowing out of the male taper). This prevents misconnection. A self-inflating bag (Ambu International, Søndre Ringvej 49, DK-2600 Glostrup/Copenhagen, Denmark), is used for ventilation with the Ambu E non-rebreathing valve. This has a resistance less than 0.1 kPa at a flow of 10 litre min^{-1} during inspiration and expiration, and a resistance of less than 0.2 kPa during inspiration and 0.25 kPa during expiration at a flow of 40 litre min^{-1}.

For paediatric use, the Ambu Paedivalve is used with a resistance of less than 0.05 kPa during inspiration, and less than 0.1 kPa during expiration at a flow of 5 litre min^{-1}. At a flow of 15 litre min^{-1} the resistance is less than 0.25 kPa during inspiration and less than 0.04 kPa during expiration.

The patient system is connected as shown in figure 3. By combining the anaesthetic equipment as shown, the following variations exist in gas supply to the vaporizer system:

(a) Oxygen rich gas from the oxygen concentrator via the oxygen rotameter.

(b) Oxygen rich gas from the concentrator mixed with air from the oxygen concentrator.

(c) Oxygen from a central supply via the oxygen flowmeter.

(d) Oxygen from a large cylinder via the oxygen flowmeter.

(e) Oxygen from a D or E cylinder on the unit via the oxygen flowmeter.

(f) Oxygen as in (c), (d) and (e) mixed with air from the concentrator via the air flowmeter.

(g) Nitrous oxide from central supply, large cylinder or from a D or E cylinder on the unit, via nitrous oxide flowmeter mixed with oxygen as specified in (a), (c), (d) and (e).

(h) If compressed gases fail, anaesthesia may be carried out with room air alone, fed through the low pressure valve on the vaporizer console.

Servicing of the equipment

An indispensible part of the project was the establishment of three store house–service centres, one in each region of the country. These are equipped with tools, turning lathes, drilling machines, electronic tools, etc. Three years' supply of spare parts were supplied with the equipment, in addition to a tool kit for each hospital for minor repairs. Spare parts for another 2 years' use have been supplied recently.

Two service technicians have been trained in Denmark for 3 months, and six more have received a 4-week training locally.

Field monitoring of the oxygen concentrators

Testing of the Malawi Anaesthetic Equipment *in situ* began in December 1986 when the first three units were installed at two different hospitals. The remainder (42 anaesthetic machines and 102 oxygen concentrators) arrived in Malawi in March 1987 and the project started at all Government hospitals soon after. By the end of April 1987, all Government hospitals in Malawi used the same anaesthetic equipment.

After installation of the equipment, follow-up visits have been made to every district, central and general hospital twice a year to evaluate the performance of the oxygen concentrators, solve any problems which have arisen and to advise and teach the staff.

A total of 1125 measurements on 75 oxygen concentrators have been made to test their performance at different flows using Datex OT 101 oxygen analysers (Instrumenta Corporation PO Box 357 SF 00101 Helsinki 10, Finland) (table I). Over a period of 26 months, all concentrators have worked according to specification. The concentrators have a build-up time of 10 min before they produce 95% oxygen. After 3 min, they produce a concentration of 68% oxygen.

If the combination of oxygen and air is used, it is now established routine at district hospitals to use a fixed flow of oxygen of 2 litre min^{-1}. The oxygen concentrator produces 95% oxygen at 2 litre min^{-1} while also providing a flow of air up to 7 litre min^{-1} (fig. 4). At greater flows of air, the concentration of oxygen decreases significantly.

TABLE I. *Readings of mean* (SEM) *oxygen concentration of 74 oxygen concentrators, during 26 consecutive months (April 1987–June 1989).* n = *Number of readings*

Flow (litre min^{-1})	Oxygen concentration (% v/v)
2 (n = 450)	95 (0.02)
4 (n = 450)	92 (0.03)
6 (n = 225)	65 (0.42)

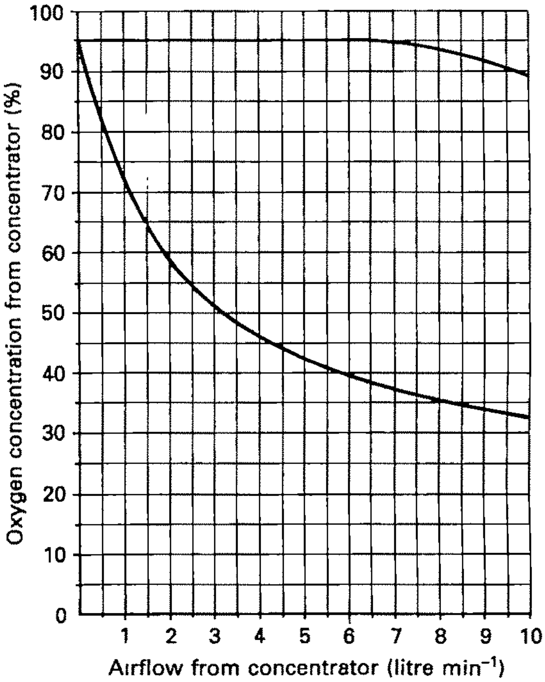

FIG. 4 Decrease in oxygen concentration both with increase in flow of oxygen with gas (lower line), and with an oxygen-rich gas flow of 2 litre min^{-1} (upper line).

When concentrated oxygen and nitrous oxide are used together it is a rule that the concentrator oxygen flow should not exceed 4 litre min^{-1} to prevent hypoxia.

Savings

The majority of district hospitals are now self sufficient for oxygen. The oxygen concentrators have been working for 26 months with a total of 97218 working hours. The calculated average flow to operating theatres and wards is 3.33 litre

TABLE II. *Savings on the Health budget resulting from the installation of oxygen concentrators at all Government Hospitals in Malawi (average values per month over 26 consecutive months (April 1987–June 1989)).* † *Calculated average flow of 3.33 litre min^{-1}. £ = pound sterling*

	General and Central Hospitals	District Hospitals	All Hospitals
Hours of operation	2437	1302	3739
Oxygen produced by concentrators (litre)†	486912	260139	747051
Cost of oxygen produced if bought in 48-ft^3 cylinders (£)	1387	741	2128
Cost of electricity at £22 MWh^{-1} (£)	21	11	32
Saved from not buying oxygen cylinders (£)	1366	730	2096
Saved on transport of oxygen cylinders (£)	2451	6884	9335
Saved on transport of patients (£)		8076	8076
Total savings per month (£)	3817	15690	19507
Total savings per year (£)	45804	188280	234084

min^{-1}, with a calculated total production of oxygen 19424156 litre.

If a hospital had bought this quantity of oxygen in 48-ft^3 cylinders (£3.874/48 ft^3 cylinder), the cost would have been £55328 (sterling). The oxygen concentrators have a power consumption of 0.4 kW. Allowing for the cost of electricity in Malawi, this produces net savings in the 26-month period of £54496; this excludes additional savings on transport.

During his stay in Malawi, one of the authors (J.P.), collected data on the frequency of transport of oxygen cylinders, and of patients transferred because of lack of safe anaesthesia at the district hospitals. Before the introduction of the Malawi Anaesthetic Equipment, the district hospitals collected oxygen cylinders an average of 2.50 times per month per district hospital. After April 1987, oxygen cylinders were collected only 0.21 times per month per hospital. In addition, fewer patients were transferred from the district hospitals to the central hospitals. The central hospitals now receive 1.8 patients fewer per district hospital per month.

Before the project, district hospitals spent £12933 per month on transport of oxygen and patients per month. As a result of the installation of the Malawi Anaesthetic Equipment, the transport expenditure has been reduced to £4127 per month—a total saving of £8806 per month for the 20 district and one general hospitals.

The total savings for the health budget is approximately £19607 per month or £234084 per year (table II), as a result of the countrywide installation of an anaesthetic system, especially designed to suit the needs of a developing country.

DISCUSSION

The total budget for this project, including 101 oxygen concentrators, 45 anaesthetic machines, three store and service centres, tools, spares for the next 5 years, training of two technicians in Denmark and six trained in Malawi has been £800000. The £234084 savings on the health budget as a result of the installation of the new anaesthetic equipment at all government hospitals in Malawi amounted to 2.16% of the total health budget of £10817131 for the fiscal year 1987/88 (information from Ministry of Health, Malawi).

Installation of anaesthetic equipment with oxygen concentrators supplying oxygen, both in theatre and various wards (maternity, paediatric and medical wards), could be a financially viable solution to many of the problems which exist in Anaesthetic Departments in any developing country, where the oxygen supply is irregular and costly. Furthermore, mortality rates have decreased significantly at the district hospitals in Malawi, especially in maternity and paediatric wards.

The design of the Malawi Anaesthetic Equipment makes it easy to use with a low pressure ventilator instead of manual ventilation, provided the drawover vaporizer console with its pressure limiting valve is replaced by a pressure vaporizer. A Manley Ventilator has been connected to an oxygen concentrator for almost 1 year at one district hospital. The unit is used on both medical and paediatric wards and is working satisfactorily.

The problems which we anticipated in using oxygen concentrators in a developing country in the tropics included the effects of high relative humidity during the rainy season and the high content of dust in the air in the dry season. To prevent water getting into the flowmeter of the anaesthetic machine, a small watertrap was added at the bottom of the buffer tank of the oxygen concentrator. The water has to be drained daily and it proved no problem for staff to remember to do this. Corrosion caused by high humidity affected three of the 45 initial vaporizes. These have been replaced and all new vaporizers are treated against corrosion; this has proven effective. The three standard filters at the air intake have proved sufficient to keep dust out of the concentrator.

Since September 1989, one oxygen concentrator has been connected to solar cells at a mission hospital in the bush. Until now this unit has performed satisfactorily. Although it is too early to base further recommendations on experience with this unit, if it continues to function well, it promises new opportunities for third world countries where electricity may be scanty and unreliable. The use of solar power also reduces running costs further.

When embarking upon the task of supplying a developing country with new standarized anaesthetic equipment, future supply of spares and the training of technicians are probably the most important considerations. Equipment around the world worth many millions of pounds is currently not being used because of absence of such simple spare parts as nuts and bolts.

ACKNOWLEDGEMENTS

We thank Anaesthetic Officers Fyson Mainjeni and Samson Nkomba for invaluable support, the Ministry of Health for their excellent co-operation and also Danida and Simonsen & Weel. We are particularly grateful to Mr Jes C. Boye-Moller, Head of Danida Mission, Harare, Zimbabwe.

The drawings in figures 1, 3 and 4 are the property of Simonsen and Weel, and reproduced here with their permission.

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British Journal of Anaesthesia 1991; 66: 271–274

CORRESPONDENCE

MASSETERIC MUSCLE SPASM

Sir,—We read with interest the recent paper by Leary and Ellis investigating the phenomenon which is often described as masseteric muscle spasm, following administration of suxamethonium [1]. Research in this area is very important because suxamethonium, with its unique properties combining, in most cases, a very fast onset of profound paralysis with a rapid termination of its action, continues to be used widely in clinical practice. It is disappointing that the authors have failed to define some terms, leading to confusion as to what they were measuring.

The accepted definitions of the relevant terms are:

Muscle tone—the resistance offered by a muscle during passive joint movements which act to stretch the muscle. It therefore comprises two elements: a passive element resulting from the natural elasticity of the muscle being stretched, and an active resistance to the stretch generated in the monosynaptic stretch reflex arc. This implies that the measurement of muscle tone must be dynamic.

Myotonia—the inability of a muscle to relax after contraction. It is a result of the repetitive firing of muscle fibre action potentials in disease states arising from instability of the plasma membrane of the muscle. This implies that electromyographic evidence of this phenomenon is necessary to be sure that it is occurring.

Spasm—an involuntary tetanic contraction of skeletal muscle generated by neural activity, often as a result of severe pain. This suggests that a paralysed muscle cannot be in spasm.

Contracture—an involuntary contraction or shortening of skeletal muscle induced usually by chemical/pharmacological agents. This is mostly an effect directly on muscle fibres, with no neural involvement.

The authors used a variety of terms, sometimes interchangeably. For example, the "myotonometer" described in the paper is not measuring muscle tone, because this can only be measured as a response to movement; instead, it is measuring some aspect of the contractile force generated during initial depolarization of the muscle fibres. An increase in muscle tone *per se* would not lead to shortening of the muscle, although the effects of myotonia would. If electromyographic measurements had been combined with this measurement and had shown repetitive firing of the muscle fibres with the increased force, then suxamethonium may have been shown to be producing myotonia in the masseters.

The patient dismissed in the paper as having "no increase in tone" but whose mouth could not be opened, is a most interesting case. In the absence of electromyographic data, the phenomenon is difficult to interpret, but could have been caused by a very large increase in muscle tone. This might be the problem encountered in clinical practice and called masseter spasm.

There have been many explanations for the abnormal responses to suxamethonium. Theories include hydrolysis of the drug before administration because of incorrect storage, and that attempts at intubation have been made prematurely, before the drug has had time to work. It could be argued that the investigation of such phenomena should begin by studying the response of the masseters to clinical doses of suxamethonium injected over a period of about 1–2 s, as in clinical practice. Ellis and Leary may be observing responses which are not relevant to clinical practice by diluting the drug and injecting it over 5–10 s, especially in the lower dose of 0.25 mg kg^{-1}. Communication of the results of these studies would be facilitated also by adherence of the investigators to conventional definitions and use of the appropriate measurement.

M. C. DERRINGTON
J. J. A. SCOTT
Leicester

REFERENCE

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Sir,—In the correspondence of Drs Derrington and Scott, although their definitions have scientific merit, in the clinical setting it is very difficult to distinguish between the various situations. The basis of our paper was to indicate and clarify the clinical problem, and the measuring techniques we used were designed to have clinical relevance rather than to elicit the pathophysiology of the situation. The terms we used were those that appeared in the literature and which did not imply exact causation of the phenomenon by suxamethonium. I repeat, our paper was not designed to elicit this causation.

Drs Derrington and Scott have made some interesting observations about future lines of research in this area, with which we fully agree, in particular the usage of electromyographic data.

Their opinion that our method of delivery of suxamethonium was unrelated to clinical practice may well be justified. However, a consistent mode of delivery for the different doses of suxamethonium was considered to be a better way to achieve pharmacokinetic compatibility.

N. P. LEARY
Melrose

INTRATHECAL MORPHINE-6-GLUCURONIDE

Sir,—The paper by Hanna and colleagues [1] raises important issues which need to be addressed.

The dose of intrathecal morphine used was very small. Regular clinical use of intrathecal morphine in cancer patients shows a ratio of 1:25 for intrathecal to oral dose. Appropriate doses for the patients in this study would have been 2.4, 4 and 20 mg, respectively, and not 0.5 mg as used. The dose chosen was confirmed to be non-analgesic by the significant consumption of pethidine.

The results from three patients cannot be used to obtain valid means and standard deviations or used for pharmacokinetic analysis, therefore these interpretations are meaningless. Additionally, the conclusions drawn by the authors are not a correct interpretation of their own data. In patients Nos 1 and 3 the consumption of pethidine was the same or less in the morphine groups 6 h after administration. Morphine-6-glucuronide (M6G) was of greater analgesic potency only in patient No. 2 at this time. There is marked irregularity in the cumulative dose in all patients, implying that perhaps other aspects were involved. What about diurnal rhythms in these individuals? Why is there delayed analgesic potency in the M6G groups—is it perhaps because M6G is deglucuronated to morphine to be analgesic?

Finally, under what circumstances were the patients selected to have their analgesia discontinued and replaced by a less potent opioid and then to have temporary intrathecal catheters inserted? Was it to improve the analgesia for these patients or solely for the purpose of a trial?

P. A. Hardy
Cheltenham

1. Hanna MH, Peat SJ, Woodham M, Knibb A, Fung C. Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine. *British Journal of Anaesthesia* 1990; **64**: 547–550.

Sir,—We are grateful for the opportunity to reply to Dr Hardy's letter.

We were intrigued that he regards intrathecal morphine 0.5 mg as a sub-analgesic dose, and would be interested in any controlled scientific evidence he has to support an intrathecal: oral potency ratio of 1:25 in chronic cancer patients. Other clinicians experienced in this field have found that the institution of intrathecal morphine at only 0.5–1 % of the oral dose results in improved analgesia [1], and previous studies of cancer patients have used intrathecal morphine 0.5 mg to good effect [2, 3]. The total consumption of pethidine during the morphine limb of our study ranged from 140 to 580 mg day^{-1}, which can not be regarded as "significant".

It is our experience that the oral: intrathecal morphine potency ratio varies considerably between patients, and it is not uncommon to see patients who, despite large oral doses of morphine and high serum concentrations have poorly controlled pain and low, or even undetectable, CSF concentrations of morphine, morphine-6-glucuronide (M6G), or both. They often respond well to very small intrathecal doses of morphine. An example of the variation in response is seen in our paper in that the patient receiving the highest oral morphine dose required the least pethidine during the morphine limb.

We were aware, of course, that more patients are needed in order to establish the exact potency and CSF kinetics of intrathecal M6G, and of the many factors which may affect analgesic requirements. We have investigated the pharmacokinetics of intrathecal morphine and M6G in a further three patients and the results obtained support our published data. The free use of a PCA system allows the patient to titrate analgesia to their desired activities, and produces marked variation in dose requirements throughout the day, as seen here. The use of a crossover design, standardized dosing times and assessment by cumulative PCA requirements up to 24 h for each drug minimizes these factors.

We doubt if deglucuronidation of M6G is responsible for delayed onset of analgesia, as administration of intrathecal M6G did not result in the production of detectable CSF concentrations of morphine. It could simply be explained by the physicochemical properties of M6G (the onset being related to lipophilicity of the drug).

All three patients who took part in this study had residual pain combined with unacceptable side effects, a situation in which we consider spinal opioids or use of a PCA system, or both, clinically appropriate (not "solely for the purpose of the trial"). Indeed, under these circumstances we would consider it unethical **not** to offer the patient spinal analgesia if facilities for this are available. Entry was considered only following informed consent and independent patient counselling, as is our usual practice. At all times during the study the patients scored pain as nil or mild, and the limits set on the PCA systems were never reached (a considerable improvement in pain control from the patient's point of view!).

M. H. Hanna
London

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SPINAL ANAESTHESIA WITH HYPOBARIC BUPIVACAINE

Sir,—I read with surprise the article by Drs Taivainen, Tuominen and Rosenberg [1] in which a relatively large volume of markedly hypobaric bupivacaine was given to patients in the sitting position. Perhaps not surprisingly, the study was abandoned because of an unacceptably high incidence of dangerously high blocks. In past times when hypobaric solutions were commonly in use, the standard procedure was to place the patient in a head-down position and gain height of anaesthesia by use of increasing volume. This article flies in the face of this conventional teaching.

I was surprised that the authors made no reference to the traditional teaching, or explained their reasons for ignoring it, even though it was shown ultimately to be justified.

R. H. James
Leicester

REFERENCE

1. Taivainen T, Tuominen M, Rosenberg PH. Spinal anaesthesia with hypobaric 0.19% or plain 0.5% bupivacaine. *British Journal of Anaesthesia* 1990; **65**: 234–236.

Sir,—Thank you for the opportunity to respond to Dr James's comments on our paper.

The cephalad spread of spinal anaesthesia with plain (slightly hypobaric) 0.5% bupivacaine is characterized by great interindividual variation of the block [1]. Several attempts have been made to achieve better prediction of the high levels of anaesthesia which would be suitable especially for abdominal surgery. These include keeping the patient in a sitting position during and after injection and increasing the anaesthetic volume from 3 ml to 4 or 5 ml. In the textbook by Lund, *Principles and Practice of Spinal Anaesthesia* [2], hypobaric techniques with volumes up to 20 ml injected with the patients in a sitting position are recommended for upper abdominal surgery because of the accurate control of the spread of the solution in the subarachnoid space.

Stienstra and co-workers [3] demonstrated in their excellent study that with a solution of 0.5 % plain bupivacaine warmed to 37 °C, thus decreasing its baricity (0.9990 at 37 °C), and injected in 15 s with the patients sitting during and for 3 min after the injection, a significantly higher cephalad spread was achieved, with less variation in the level of analgesia than after use of a solution at room temperature. In our present study we wished to investigate if the same effect would result with a bupivacaine solution that was made hypobaric by diluting it with water and injecting it at room temperature. The volume used, 3 ml of 0.5 % bupivacaine + 5 ml of distilled water (baricity 0.9927 at 21 °C), was significantly smaller than that recommended in Lund's textbook. The sitting period, 40 s for injection and 2 min after it, was shorter than in Stienstra's study. Otherwise, a design similar to that in Stienstra's study was planned.

We do appreciate conventional teaching in addition to the concepts learned from development of clinical anaesthesia. We are sorry that we could not include older references in the text, mainly because of editorial reasons. Because the aim of our study was to elucidate the properties of bupivacaine, we referred only to the most recent papers.

It is evident that the optimal solution of bupivacaine for spinal anaesthesia is still unknown and modifications of the existing solution have to be considered in future research.

M. TUOMINEN
T. TAIVAINEN
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BLIND NASAL INTUBATION THE ONLY OPTION?

Sir,—Experience of blind nasal intubations in patients similar to that described by Dr Suresh [1] suggests that the tracheal tube (or fibrescope) should always be inserted through the nasal passage on the side opposite to the mass. There may be little relation between the swellings externally and internally. The pharynx may be normal, or the ipsilateral pharyngeal wall may bulge towards or even across the midline, and thereby interfere with or prevent a tube (or fibrescope) inserted through the nose on the same side from approaching or entering the glottis. Other potential risks include trauma or perforation of any internal mass, with release of pus, initiation of bleeding, or the creation of a false passage. It would also seem mandatory to insert a cuffed tracheal tube in all such cases of trismus to protect the airway in the absence, and until the introduction, of a pharyngeal pack. Airway management should anticipate the worst scenario because laryngoscopy may reveal nasty surprises!

The following example allowed no such latitude: after several serious bleeding episodes, a 16-yr old youth required exploration of a shotgun injury to the left face (involving mouth and pharynx) sustained and debrided surgically 6 days earlier. Following preoxygenation by mask, the patient was positioned steeply head-down and cricoid pressure applied with a thiopentone–suxamethonium induction. As laryngoscopy was performed, massive bleeding occurred, filling the pharynx, mouth and nose and rapidly forming a pool on the floor. As suction would not have helped, the only immediate available option for ensuring and protecting the airway and the patient's survival seemed to be blind intubation. This was unsuccessful with the tracheal tube alone, but was achieved with a stylet curved cuffed tube pernasally [2]. The left external carotid artery was ligated, tracheotomy performed, and the wound and pharynx packed firmly, but heavy bleeding persisted. On re-exploration, a large perforation of the right common carotid artery was found and repaired

It should never be said that blind nasal intubation is unsuitable or unsuccessful unless it has been tried. Tracheal intubation may be surprisingly easy, as Dr Suresh notes [1], even with what appear to be rather difficult intubation problems [3].

R. WILLIAMSON
Natal, South Africa

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DOMICILIARY OXYGEN CONCENTRATORS IN ANAESTHESIA

Sir,—The article by Wilson, Van Heerden and Leigh [1] describing the use of oxygen concentrators for preoxygenation during drawover anaesthesia was a very useful addition to the literature. We shall certainly add a black bin-liner to our Tri-service Anaesthetic Apparatus! However, I should like to point out that the formula proposed is not as original as the authors imply, and is a simple modification of the equation described originally by Mackie [2]. In addition, Mackie investigated other variables affecting the $F_{I_{O_2}}$ in a drawover system which are not discussed by Wilson and colleagues and are important in the application of the formula, namely, ventilator frequency, I:E ratio and reservoir size. It is necessary, therefore, to point out that the formula is an approximation only, particularly when considering that, without direct measurement, one cannot rely on either the $F_{I_{O_2}}$ or the flow rate delivered by the oxygen concentrator.

S. Q. M. TIGHE
Gosport

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Sir,—We thank Surgeon Lt Commander Tighe for his helpful comments regarding the above article.

The formula described by Mackie [1] for calculation of $F\mathrm{I}_{\mathrm{O}_2}$ during drawover anaesthesia is a simple one for the mixing of two volumes of gas with known $F\mathrm{I}_{\mathrm{O}_2}$—namely oxygen from a cylinder ($F\mathrm{I}_{\mathrm{O}_2}$ 1.0) and atmospheric air ($F\mathrm{I}_{\mathrm{O}_2}$ 0.21). Mackie makes the point in his article that $F\mathrm{I}_{\mathrm{O}_2}$ is therefore dependent mainly on oxygen flow, reservoir volume and total ventilation. Ventilatory frequency and I:E ratio have only a small influence. We would concur with this view.

Our own formula for prediction of $F\mathrm{I}_{\mathrm{O}_2}$ includes a correction for variation in $F\mathrm{I}_{\mathrm{O}_2}$ of the added concentrator "oxygen". In practice, the variation in oxygen output from the concentrator is predictable, provided that adequate "warm-up" time elapses and, in fact, varies comparatively little between different makes of concentrator. Our sole claim to originality with respect to this formula is that we wrote it down first!

Incidentally, the colour of bin-liner used is not relevant to the formula!

J. Leigh
Bristol

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PROPOFOL SUPPORTS BACTERIAL GROWTH

Sir,—Recent reports of multiple postsurgical infections following the use of propofol [1] stimulated me to ask our hospital laboratory to perform a simple bacteriological study.

Containers of 2.5% thiopentone and 1.0% propofol were inoculated separately with standard bacterial cultures of *E. coli* ATC No. 25922, *Pseudomonas aeruginosa* ATC No. 27853 or *St. aureus* No. 29213 and incubated for 24 h. All three organisms grew vigorously in the propofol, but not at all in thiopentone.

For interest, I measured also the pH of the two agents. The results were: propofol 3.5, thiopentone > 8.

It is thus important for all of us to know that propofol is a fertile medium for bacterial growth, therefore anaesthetists should be careful in handling and preparing it. It would seem that it should be drawn up from the sterile ampoule only a few moments before injection, and not stored in the syringe for hours or days.

D. V. Thomas
Los Altos, California

ACKNOWLEDGEMENT

I am indebted to Dr F. Elevitch and Ms Barbara Fagundes of El Camino Hospital, Mountain View, California for helping with these tests.

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NAARAS: THE ADVISORY SERVICE TO ANAESTHETISTS PROVIDED BY THE SUPRAREGIONAL PROTEIN REFERENCE UNIT IN SHEFFIELD

Sir,—Advice based on the analysis of laboratory and clinical data from patients exhibiting life threatening anaphylactoid response has been provided from this laboratory since 1973. Reactions were and are reported from all the Health Regions of the U.K. In 1989, some 200 patients were investigated in depth and a similar number commented on only in terms of clinical report. We believe that the majority of anaesthetists have been satisfied with the service provided; we apologize to those for whom the service has proved less than adequate.

The analysis has proved costly. Incorporating the latest assays for plasma tryptase release and RAST assay has increased the cost of analysis to almost £100 per patient. This has largely been met from donations from the pharmaceutical industry, although we warned in 1989 that the service could not continue without centralized funding or support. The situation has now become critical.

The working party of the Association has now reported upon the problem of anaphylactic reactions. It provides clear advice for patient management and laboratory follow up. The latter should be undertaken at local level and anaesthetists should now make the necessary arrangements with the appropriate Department of Immunology. Accordingly, the centralized advisory service operated from Sheffield as "NAARAS" will be discontinued as from January 1, 1991.

J. Watkins
Sheffield

DIMETHYLTHIOUREA IS NOT NECESSARY TO PREVENT THE EFFECTS OF NITROUS OXIDE INACTIVATION OF METHIONINE SYNTHASE

Sir,—In their paper, Koblin and Tomerson [1] mentioned the occasional haematological and neurological effects of nitrous oxide as a result of its possible inactivation of methionine synthase. Such sequelae are frightening, particularly when the authors concluded also that dimethylthiourea, although impeding this inactivation, is unlikely to be a suitable agent for clinical prevention of this action of nitrous oxide.

However, this is really not a problem, because the deleterious sequelae following exposure to nitrous oxide occur only following exposures of 5 h or more in the healthy non-debilitated individual [2], and, even in compromised patients, these consequence may be prevented if adequate doses of folinic acid (leucovorin) are given [2, 3].

M. A. Gillman
Johannesburg

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methionine synthase by nitrous oxide. *British Journal of Anaesthesia* 1990; **64**: 214–223.
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Sir,—The main purpose of our paper was to test further the hypothesis that nitrous oxide combines with the vitamin B_{12} molecule of methionine synthase to form a hydroxyl radical that reacts with and inactivates the enzyme. Our results were consistent with this hypothesis [1]. I agree with Dr Gillman that harmful sequelae rarely occur in healthy individuals after clinical administration of nitrous oxide, even though more than 50 % of hepatic methionine synthase is inactivated after a 2-h exposure to 50–70 % nitrous oxide [2, 3]. In those patients known to have severe deficiencies in vitamin B_{12}, folate, or both, it is advisable to correct these vitamin deficiencies and to avoid administration of nitrous oxide.

D. D. Koblin
San Francisco

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MINITRACHEOTOMY—IMPOSSIBLE CANNULATION

Sir,—Minitracheotomy (MT), described initially by Matthews and Hopkinson [1], is a method for treating bronchial congestion. Until now, few complications have been reported [2, 3]. The following is a description of two patients in whom catheter insertion was impossible because the cricothyroid space was too small.

Patient 1. A few days after insertion of a ventricular-peritoneal shunt for hydrocephalus, a 60-yr-old female presented severe bronchial congestion. Because of the patient's poor neurological status it was decided to perform MT under local anaesthesia using the percutaneous technique. Although insertion of the leader was easy, cannulation was impossible. In order to assess the cause of this difficulty, it was decided to expose the cricothyroid space surgically. The height of the space was 4 8 mm—smaller than the external diameter of a standard cannula. MT was therefore not performed.

Patient 2. After undergoing 28 days of mechanical ventilation for bacterial pneumonia, a 62-yr-old male presented with severe bronchial congestion and MT was attempted in order to permit tracheal extubation. The technique used was similar to that in patient 1. Insertion of the leader was easy, but cannulation was impossible. Because surgical exploration revealed a cricothyroid space of 5 mm in height, MT was not performed.

MT by the standard percutaneous method is usually easy However, difficulties can be encountered because of the anatomy of some patients (short, fat neck), especially females [4], or because of calcification of the cricothyroid membrane which may follow previous MT. Failure of cannulation because of a small sized cricothyroid space has not been reported previously.

Forced insertion of the cannula may cause cricoid cartilage lesions leading ultimately to severe subglottic stenosis [4]. Caparosa and Zavatsky [5], studying 51 adult larynxes, found a mean sagittal height of the cricothyroid space (between the antero-inferior edge of the thyroid cartilage and the antero-superior edge of the cricoid cartilage) of 9 mm (range 5–12 mm). Carter and Meyers [6] found slightly smaller dimensions in the female. Thus in most patients the cricothyroid space is larger than the MT cannula, which has an external diameter of 5.4 mm. In some subjects, especially in females, this space may be smaller than the cannula, but in the two patients reported, clinical examination did not permit anticipation of this difficulty.

We suggest that, when cannulation is difficult by the standard method, surgical exploration should be attempted in order to verify the size of the cricothyroid space.

P. Combes
J. P. Gayard
B Fauvage
Grenoble

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British Journal of Anaesthesia 1991; **66**: 276–279

BOOK REVIEWS

Resuscitation and Training. Edited by A. Bristow, V. Dallos and G. Hanson. Published (1989) by Farrand Press, London. Pp. 263; indexed; illustrated. Price £19.80.

This is a multi-author book but the three editors have written most of it, with four guest authors contributing a chapter each. The book is a slight disappointment in that it does not flow well—there are differences in writing styles and printing types. Some of the tables appear to have been photocopied from other publications and the basic life support diagrams are copies from the Resuscitation Council booklet with Laerdal diagrams. This is not inappropriate, but I could find no acknowledgement.

The book starts with a scanty description of the pathophysiology of cardiac arrest and then goes through basic and advanced life support techniques in some detail, including guidance in practical procedures. There are chapters on resuscitation in special circumstances and for the neonate, child and pregnant woman. There is a good section on recommended equipment for the General Practitioner.

There are several irritating errors and omissions in the book. Nowhere is there a mention of the semi-automatic advisory defibrillator, surely one of the most important developments in cardiopulmonary resuscitation (CPR) in the past 5 years. There are several spelling mistakes and the defibrillation procedures, in quoting the Resuscitation Council (U.K.) *Guidelines*, use the outdated quoted energy values as 400 J rather than 360 J. Ventilation through needle cricothyroid membrane puncture does not mention the need to ensure that exhalation is feasible through the larynx and mouth.

The best part of the book is at the end, and describes the Whipps Cross Hospital experience with CPR training. There is much to learn here, with guidance given on CPR advisory committees, Resuscitation Training Officer job descriptions, CPR Audit techniques and outline of Training Programmes for all, ranging from the public to the specialist hospital doctor. There is a great deal of detail about training programmes, with time and subject schedules, equipment and instructor requirements and testing methods all carefully set out. Many will want to copy the very useful MCQs for Basic and Advanced Cardiac Life Support, including neonatal, paediatric and obstetric patients. I would buy the book particularly for the last 90 pages.

P. J. F. Baskett

Ventilation/Blood Flow and Gas Exchange, 5th Edn. By J. B. West. Published by Blackwell Scientific Publications, Oxford. Pp. 120; indexed; illustrated Price £9.95.

This clearly written book gives a lucid account of the causes and effects of mismatching of ventilation and perfusion within the lung. The concepts were developed by a talented group of American physiologists at the end of the Second World War and then presented lucidly by Julius Comroe in his wonderfully illustrated book *The Lung* (1955), which influenced a whole generation of respiratory physiologists. John West then entered the field, developing and exploiting entirely new technology. He moved away from the "three-compartment model", based on deductions from blood-gas values, to actual measurements of ventilation and perfusion in the real lung This book takes the reader through these classical studies and explains the relevant theory and measurements with great clarity. However, the reviewer remains concerned that the casual reader may confuse the vertical spread of ventilation/perfusion ($\dot{V}/\dot{Q}$) relationship shown on the front cover with what happens during normal breathing. The now famous range of values for $\dot{V}/\dot{Q}$ ratios from 3.3 at the top of the lung, down to 0.63 at the bottom, was observed during a slow vital capacity inspiration. The inequality is much less marked during normal tidal breathing from the functional residual capacity, particularly in the supine position.

A fifth edition invites comparison with earlier editions. There is, in fact, very little difference from the fourth edition. The figures are identical and, apart from a few very minor changes to enhance clarity, the only new text is a one-and-a-half page introduction to the multiple inert gas elimination technique (MIGET), the remainder of Chapter 6 being identical to the text in the previous edition. There is only one new reference, and the list of suggested reading still contains nothing after 1964, apart from three works by the author himself.

The message is clear. This book is essential reading for every serious student of the lung. However, it is insufficiently changed from the previous edition to warrant a new purchase by those who already have the earlier edition.

J. F. Nunn

Patient Controlled Analgesia. Edited by F. M. Ferrante, G. W. Ostheimer and B. G. Covino. Published by Blackwell Scientific, Boston, Oxford. Pp. 244; indexed; illustrated. Price £32.50.

There can be no doubt that patient-controlled analgesia is rapidly becoming a popular method for the treatment of postoperative pain. After the first international workshop on PCA held at Leeds Castle, Kent in 1984, a book describing the proceedings was published. This has been a very useful text and is well known to those interested in PCA. However, this is now largely out of date and the book under review is an attempt to correct this. It is not a second edition of the first book; the contents and authors differ substantially.

The chapters are arranged in four parts. Part I gives a historical and scientific background to PCA. Chapters describe the background to postoperative pain, pharmacology of opioids, the various PCA systems available and the use of PCA as a research tool. Part II concentrates on the clinical use of PCA and describes authors' experiences of this technique in several situations including postoperative pain, obstetrics, paediatrics and oncology. There is also a useful chapter outlining complications that have arisen with PCA. Part III concentrates on logistic and economic factors. For the U.K. reader, the problem with this section is that it describes experiences in the U.S.A. only. The final section is entitled "The Future". Chapters describe potential pharmacological developments, new PCA systems and methods of administration of PCA.

This book is a comprehensive and reasonably up-to-date review of most aspects of PCA. There are approximately 30 authors and many of them are recognized experts. However, it is a pity that not a single author is a U.K. practitioner. This is in stark contrast to the previous book produced by the same publishers 6 years ago.

However, most of the chapters are well written, precise and thoughtful. It would be a very useful book to have available in departments where PCA is used.

D. J. Rowbotham

Major Chemical Disasters—Medical Aspects of Management, 1st Edn. Edited by V Murray Published by The Royal Society of Medicine Services Ltd, London. Pp. 204; illustrated. Price £15.00.

This publication is a compilation of the papers presented at an international meeting held at the Royal Society of Medicine in 1989. The book represents one of the most comprehensive publications on the subject, with contributions from acknowledged experts in the U.K. and from other countries. It has been very well edited.

Major chemical accidents which have occurred in the past are reviewed and errors of management are highlighted in the opening section. This is followed by three papers which address the future in terms of likely incidents and their prevention and possible impact on the environment. There is a first class section of 10 papers covering the immediate responses to a large chemical incident by the emergency services, accident and emergency department and poison centre, together with the planned response by local authority, civil defence and chemical companies. There are special contributions on communications and maritime chemical incidents

Further sections cover toxic hazard identification and risk assessment, and specific aspects of medical management of respiratory, ophthalmic, gastrointestinal and skin contamination. Finally, there is a section on epidemiological lessons learnt from Bhopal and a chapter on the psychological impact of chemical disasters.

This book is really very good indeed, and should be an essential reference book in every hospital library and accident department. It is vital reading for those responsible for planning and preparing the medical response to a chemical disaster. I am very pleased to own a copy of this modestly priced book.

P. J. F. Baskett

Anaesthesia Review 7, 7th Edn. Edited by L Kaufman. Published (1990) by Churchill Livingstone, London. Pp. 243; indexed. Price £18.50.

This is the seventh review edited by Dr Kaufman; the first was published in 1982, so new editions come out almost every year. What is the purpose of this series? It aims to review various developments which may be of interest to anaesthetists, and the editor has again placed particular importance on aspects of medicine; thus this issue deals with a *pot pourri* of medical topics, together with fuller accounts of respiratory medicine, endocrinology and renal function tests. Separate chapters consider obstetrics and paediatrics, and there is an excellent account of modern transfusion practice. There are also other good contributions such as those on electrical safety and the manufacture and uses of medical gases, although there is little new to say on both topics. The "specials" on the menu in this edition are two chapters, totalling 27 pages, on anaesthesia for liver transplantation. The editor concludes this volume as in previous editions, with an "update" on topics chosen from previous editions.

There is a reasonable amount of material of a review nature available nowadays on both sides of the Atlantic. Although the strength of this series is the ability of the editor to assemble experts who write with good practical knowledge, it is unusual to find much in the way of contributors' comments or criticisms of the topics under review and the reader is often left merely with strings of referenced statements. Nevertheless, those who have purchased earlier editions of the *Anaesthesia Review* series and wishing to add this latest volume to their libraries will not be disappointed.

A. P Adams

Advances in Pain Research and Therapy 14: Opioid Analgesia Edited by C. Benedetti, C R. Chapman and G. Giron. Published by Raven Press, New York. Pp. 494; indexed; illustrated. Price $118.

This book is the proceedings of a 2-day symposium held in Venice to celebrate the 70th birthday, in 1987, of Bonica (the doyen of American pain doctors). The Papal foreword is a unique feature. The book is divided into Fundamentals and Clinical Application. Fundamentals includes chapters from Kosterlitz on opioid receptors, Yamamura's group on multiple receptors and ligands and chapters from Mather and Stanski, Inturrisi and Tucker on kinetic and metabolic aspects of opioids. Clinical Application has a section on routes of administration, with chapters on oral, sublingual, transnasal and rectal routes, a section on sustained release formulations of oral morphine, and one on patient-controlled analgesia.

Proceedings published 3 years after the event are clearly not going to present the leading edge of research. On reading the book, I was looking for ideas and, on subjects about which I know little, for direction. The huge chapter on receptors and ligands (more than 40 pages) in necessarily the one most overtaken by events. A paper on plasticity emphasizes that diet, age and hormones may all produce functional plasticity of endogenous systems. Dr Tucker's review of the difficult topic of pharmacokinetic/pharmacodynamic models is one to which I shall turn again. I was disappointed in the chapter on tolerance and dependence There is a real puzzle lurking in the findings of up- and down-regulation in antagonist and agonist opioids, which would lead one to expect tolerance in chronic pain management with opioids, and the fact that increased drug requirement is taken clinically to mean disease progression. Does continuing pain pre-empt down-regulation?

In the clinical section I found little which is not available elsewhere, apart from the review of transnasal delivery by the Bristol-Myers team. The route may prove to be useful, although public health concerns may limit its utility for opioids. I enjoyed the two chapters from the Seattle group, one on PCA in post-transplant mucositis, and the other on tailored opioid infusions. The PCA in mucositis data are relevant to all those taking PCA into longer-term contexts; despite apparently limited efficacy, the outcome was still substantially better than that achieved by conventional opioid delivery.

Overall, then, a book of shreds and patches. Presumably a marketing genius has decided that having an incomplete series on the shelves drives us all out to the bookshop. Although that motive is to be despised, this series is useful as source material, and there are chapters in this volume which maintain that reputation.

H. J McQuay

Fiberoptic Airway Endoscopy in Anesthesia and Critical Care. By A. Ovassapian. Published by Raven Press, New York. Pp. 192; indexed; illustrated. Price $126.00.

Over the past decade, use of the fibreoptic scope to aid tracheal intubation has increased considerably. Anesthetists are recognizing the practical value of these instruments and are becoming familiar with the techniques associated with their use. Anaesthetic departments throughout the U.K. are purchasing fibreoptic equipment for routine clinical practice. Concomitant with this expansion in use is the need to establish training schemes to allow junior anaesthetists to become competent in the use of fibreoptic technology. This 172 page book covers comprehensively the whole area of fibreoptic airway endoscopy. It is divided into 11 very readable chapters.

The first chapter outlines the physical principles involved in the construction and design of the flexible fibreoptic endoscope. There are many useful diagrams and tables; of particular interest is a table outlining the physical properties and diameters of available adult and paediatric fibreoptic scopes. Helpful advice is given also on various light sources and photography.

Anatomy of the trachea and bronchi is discussed in chapter 2. The text is accompanied by accurate line drawings and high quality colour photographs showing views obtained of the upper and lower respiratory tract. Conventional radiology of the upper airway, computed tomography and magnetic resonance images are presented in chapter 3 There is a useful section covering cervical spine trauma, with clear accompanying x-ray pictures

The following two chapters cover in detail the crucial areas of topical anaesthesia of the airway and fibreoptic tracheal intubation. The author describes the technique used to perform tracheal intubation in the awake subject using either the oral or the nasal route. The text is illustrated with many high quality colour photographs and detailed line drawings.

Subsequently there is a description of techniques used to intubate the trachea with the fibreoptic scope in anaesthetized subjects. Various aids to fibreoptic tracheal intubation and guidewire techniques are explained. The success rate of fibreoptic tracheal intubation from a number of studies is presented, with a helpful discussion on the complications and common causes of failure.

In chapter seven, the author describes the instrument used in the intensive care unit, and reports its use in epiglottitis, smoke inhalation injury and obstructive sleep apnoea. We are also reminded of the value of the fibreoptic scope in checking the position of the tracheal tube.

The causes of a difficult airway and difficult intubation are outlined. There is a clear discussion on the management of difficult intubation. These are highlighted in chapter 10, by the presentation of a series of case reports. The final chapter provides valuable advice on the learning and teaching of fibreoptic tracheal intubation.

In conclusion, this is a valuable book which will be of interest to all anaesthetists. It is well written and has numerous photographs which illuminate the text. This is certainly a book for all anaesthetic libraries and will be bought by many anaesthetists interested in learning or teaching fibreoptic airway endoscopy.

J. Langton

Clinical Cases in Anesthesia, 1st Edn. By T. M. Tracy, K. Quinlan, A. P Reed and J. A. Kaplan. Published by Churchill Livingstone, New York. Pp. 340; indexed; illustrated. Price £22.50.

This is an unusual type of book in that it is designed very precisely to provide teaching based on selected clinical problems, with a detailed discussion of the basic science background. There are 29 cases grouped according to system affected; for example the 86-year-old man who has a cardiac arrest in the operating theatre, the patient with sickle cell disease, the complications of invasive monitoring or the management of burns. The book is suited ideally to the candidate preparing for the Part 3 F.C.Anaes. examination, but would certainly benefit the Part 1 candidate and indeed most consultants. The layout, with 10–15 questions on each case, fits the pattern of an oral or written examination answer or a tutorial in preparation for these.

Looking at the book in more detail, the reader must first accept that it is American. Thus drug names and limitations and biochemical units are often different from those most familiar in the U.K. References are mainly but not exclusively to U.S. literature, and techniques often favour American usage. However, the spelling of Sir Roboter Macintosh (p. 195) is presumaly not an attempt to americanize and automate the first holder of an anaesthetic chair in Britain. There are several similar misprints, but none which impairs the value of the book.

The authors have been at pains to update management to fit in with the best modern practice. For instance, in the case of diabetes they discuss the older practice of allowing the blood glucose to increase as a safer alternative to hypoglycaemia, and make clear that this is no longer acceptable. They discuss the safety of suxamethonium in management of the perforating eye injury and state firmly that it is the best of the alternatives. They recommend administration of platelet concentrates at an earlier stage of bleeding disorders than was formerly the practice.

Altogether, it is a most stimulating book which may be read profitably by the majority of anaesthetists, whether teaching, taught or simply keeping up to date. It is attractively printed and produced, and at a price of £22.50 should be in every departmental library

R S. J. Clarke

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

BLOOD CONSERVATION

Homologous blood is a precious resource and in the U.K. self-sufficiency in blood and blood products is dependent on voluntary contributions. Local shortages occur from time to time when heavy demand coincides with low rates of collection; a problem which could be extenuated by some methods of blood conservation. Although intraoperative blood loss may be minimized by meticulous surgical and anaesthetic technique, some procedures result in blood loss that exceeds 15–20% of the patient's blood volume, necessitating the transfusion of homologous red blood cells. As with any therapeutic intervention, the potential benefits must be weighed against the perceived risk—an analysis which involves many factors, including the patient's age, preoperative physical state and the presence and severity of any coexisting medical disease. It is well known that transfusion-related morbidity and mortality may result from either an immunologically mediated reaction or a transmitted infection; these different complications are summarized in table I.

The risks of transfusion of homologous blood are difficult to quantify and vary with the geographical area from which the blood has been donated. In general, the risk of transmission of infection depends on the relevant disease carrier rate in the indigenous population and the efficacy of screening measures. In the U.K., donor blood is screened routinely for syphilis, hepatitis B surface antigen and the human immunodeficiency virus (HIV) and thus the chance of contracting these infections via transfusion is remote. However, there is some concern about the reliability of the test for HIV, which detects antibody to the virus. This anxiety was provoked by the observations that it could take 3–6 months to develop this marker antibody and that the virus possessed a remarkable capacity for antigenic change which could result in infected individuals remaining undetected [1]. Post-transfusion hepatitis C (formerly nonA-nonB) is often a mild or subclinical, anicteric illness. It may, however, result in fulminant liver failure or a prolonged viraemia followed by a persistent carrier state. In these circumstances chronic liver damage occurs in up to 50% of patients [2]. In two large studies, the incidence of post-transfusion hepatitis C varied from 2% to 11.2% [3, 4]. Recently, a sensitive assay to detect anti-hepatitis C antibodies has become available and preliminary serological surveys of healthy donors indicate prevalence rates of 0.5–1.0% in some regions of the U.K. [5]. This test may be added to the routine screening procedures used by the National Blood Transfusion Service—an addition that could reduce the risk of transmission of this virus. However, at present there is, unfortunately, no confirmatory test available as there is for HIV 1.

In addition to these inherent but variable risks, blood is also an expensive commodity. By the time it has been collected, screened, typed, stored, redistributed, cross-matched and given to the patient, significant expense has been incurred.

It is for these reasons that there is renewed interest in methods intended to minimize the need

TABLE I. *Complications of homologous blood transfusion*

Immunological complications	
To red cell antigens	Haemolytic reactions
	Immediate
	Delayed
To white cell antigens	Febrile reactions
	Pulmonary infiltrates
To platelet antigens	Post-transfusion purpura
To plasma proteins	Anaphylaxis
Transmitted infection	
Hepatitis C	
Hepatitis B	
HIV 1 and HIV 2	
Cytomegalovirus/Epstein–Barr virus	
Syphilis	
Malaria	
Chagas' disease (trypanosomiasis)	
Human parvovirus	

for homologous blood. Currently, the only realistic alternative to homologous transfusion is the use of autologous blood, that is transfusion of a recipient with his own blood. This eliminates the risk of serious infection and also avoids sensitization of the red cell, white cell and platelet antigens in donor blood. Artificial oxygen carriers could provide a satisfactory alternative to the use of homologous blood, but although two are undergoing investigation, neither is available for routine clinical use. Polymerized, stroma-free, haemoglobin solutions appear to have characteristics similar to those of red cells, but have very brief intravascular lives [6]. Perfluorocarbon emulsions cannot hold as much oxygen as haemoglobin and require to be exposed to oxygen-enriched air. The place of these blood substitutes in clinical practice remains uncertain [7].

The concept of autologous blood transfusion is not new, having been suggested by Highmore in 1874 after he had lost a patient from postpartum haemorrhage [8]. It was used first by Duncan in 1886 and became a standard form of treatment by 1936 [9]. However, the development of safe, efficient systems for homologous blood replacement during the Second World War resulted in decreased utilization of autologous blood.

Commonly, three methods of autologous transfusion are described: preoperative deposit, preoperative phlebotomy with haemodilution and intraoperative blood salvage. Each technique requires the co-operation, enthusiasm and expertise of anaesthetists, who should be familiar with each technique and the principles involved.

Preoperative deposit. Patients scheduled to undergo elective surgery are eligible for deposit of autologous blood, providing their haemoglobin concentration is at least 11 g dl^{-1}. The shelf-life of CPD-A and SAG-M blood is 5 weeks (although it is likely that both are safe to 6 weeks, particularly SAG-M). Thus 4 units of autologous blood could be collected safely during the 5 weeks preceding surgery. Normal marrow can replace 1 unit of blood in 3–4 weeks in patients receiving iron supplements, but recent studies suggest that recombinant human erythropoietin increases further red cell production [10]. This may improve the safety margin of this process and allow its use in anaemic subjects. Those with most experience argue that anyone with normal marrow function who is fit for general anaesthesia and surgery may donate blood in an autologous programme [11].

If the programme is organized well and its availability and benefits are brought to the attention of relevant medical staff, as much as 55% of elective surgery (requiring blood) could be provided with autologous blood [12], and in 85% of patients the deposit of autologous blood would satisfy all transfusion requirements [13]. The disadvantages are logistical, as patients must attend the blood transfusion laboratory on multiple occasions and a meticulous system for labelling and storage must exist. The hazard of misidentification is as great as with homologous donor blood. However, this system is practicable if the patient lives locally and is prepared to make the necessary effort. Autologous transfusion programmes in either a district general hospital or teaching hospital in the U.K. have to be under the direction of a Consultant Haematologist [14].

Preoperative phlebotomy and haemodilution. Elective haemodilution is the process whereby 1–2 litre of blood is venesected into CPD-A packs and replaced simultaneously by an equal volume of colloid. This isovolaemic reduction in PCV decreases blood viscosity and peripheral vascular resistance and the resultant increase in cardiac output maintains tissue oxygen delivery. Surgical haemorrhage consists of haemodiluted blood and the reserved whole blood is reinfused when haemostasis has been secured, providing coagulation proteins and platelets, in addition to red cells. This method is applicable to a small number of patients, but has not gained widespread acceptance. Although experimental studies suggest that the maximum oxygen delivery to tissues occurs at a PCV of 30%, there is no agreed minimum safe haemoglobin concentration in humans, particularly those with ischaemic heart disease.

Intraoperative blood salvage. Currently, several good systems for operative blood salvage are available and they can be classified into two basic groups: those that collect and return but do not wash cells and those that collect, wash, resuspend and rapidly return washed red cells.

The two most popular systems which collect but do not wash cells are the Sorenson and the Solcotrans systems. The Sorenson system developed by Noon and associates uses a special suction tip that mixes aspirated blood with CPD anticoagulant [15]. When full, the collecting bag is attached to a standard blood administration bag and inverted for transfusion. The Solcotrans is a simple, disposable unit that consists of a reservoir containing anticoagulant attached to a suction wand via a short PVC tube. The reservoir is inverted for transfusion to the patient. As much as 5 units of shed blood may be collected without significant haemolysis or coagulopathy [16]. It may be used during operation or to collect blood from postoperative drainage, in which situation it has become popular in the U.K. These units are designed to collect the continuous, slow blood loss that is typical of many surgical procedures and their use results in the avoidance of use of homologous blood in these circumstances. In general, they are not suitable for use in severe, rapid haemorrhage.

Autotransfusion systems that rapidly collect, anticoagulate, wash and concentrate red blood cells have been available for some time and four such devices exist although only one is used commonly in the U.K. These systems comprise four primary components: a large-bore suction tube (which has a separate channel for introducing heparin), a plastic reservoir with a macroaggregate filter, a bell-shaped continuous flow washing bowl driven by a centrifuge and a transfer pack to collect and reinfuse the washed cells. Physiological saline is used to wash the salvaged red cells and remove all cellular debris, heparin and contaminants. The end result is a suspension of red cells in saline with a PCV that depends on the duration and volume of the wash (50% after a complete cycle). Autologous salvage alters blood components which are traumatized or activated to some extent by suction, tubing, filters and centrifuge. The potential adverse effects include haemolysis, shortened red cell survival, coagulation disorders, air embolism, changes in 2,3-DPG, platelet and fibrinogen loss, microemboli and the spread of malignant cells.

In the context of trauma with torrential haemorrhage, it is likely that homologous blood may still be required, because there is a limit to the rate at which shed blood can be evacuated by suction without irretrievable damage to cells. An increase in vacuum pressure to more than 100 mm Hg is likely to result in an unacceptable degree of haemolysis. In a massive haemoperitoneum, for example, large abdominal packs are needed in order to visualize the bleeding points and only a small proportion of the intraperitoneal blood collects in the suction jar. In one study, the autotransfusor provided only 28% of transfusion requirements in trauma cases [17]. Thus, paradoxically, when the need for autotransfusion is greatest, it is least effective, although theoretically it is possible to overcome this problem by increasing vacuum pressure, by having more than one reservoir (or cell saver) in series or by reducing washing time. Newer generations of cell saver will be more efficient in this situation, although all will salvage the persistent "ooze" that inevitably follows initial haemostasis.

Anaesthetists are responsible for the administration of more blood and blood components than members of most other clinical specialties. As a group, we are acutely aware of the risks involved and should be prepared to explore any feasible alternative if it might result in an improvement in the existing safety margin and the conservation of a scarce resource. Autologous transfusion avoids the transmission of infection, in particular HIV, but also the hepatitis viruses and other bloodborne pathogens. If it is to be considered beneficial and cost effective, it should provide all the patient's blood requirements at a cost comparable to existing methods. Although the benefit is reduced significantly if supplementation with homologous blood becomes necessary, even in this situation the use of autologous transfusion can be justified on the grounds of cost and conservation. In particular, it is likely that the utilization of intraoperative salvage and return will increase and it would be appropriate for anaesthetists to be involved with the purchase of the necessary equipment in addition to the supervision and training in its use.

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CONTINUOUS AMBULATORY ECG MONITORING IN THE PERIOPERATIVE PERIOD: RELATIONSHIP OF PREOPERATIVE STATUS AND OUTCOME

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SUMMARY

We have used continuous ambulatory electrocardiography in the perioperative period to monitor 108 patients with known cardiovascular disease undergoing non-cardiac surgery. There was a high incidence of ischaemic ST segment changes and ventricular arrhythmias. For the group as a whole, anaesthesia and surgery were followed by increased ventricular ectopic activity, but did not worsen myocardial ischaemia. However, the mean duration of ischaemic ST segment changes was increased significantly in those patients with treated hypertension. Of the risk factors considered, preoperative ischaemia and peroperative systolic arterial pressure were significant correlates with postoperative myocardial ischaemia.

KEY WORDS

Heart: arrhythmia, ischaemia. Monitoring· electrocardiography, Compas monitor

Cardiovascular disease, especially ischaemic heart disease, is common and present in approximately 15% of all patients undergoing surgery [1]. It is recognized that these patients are at increased risk of perioperative myocardial ischaemia [2]. The incidence of postoperative myocardial infarction in such patients undergoing non-cardiac surgery was between 5 and 18% in various studies, compared with 0.1–0.4% in patients without evidence of preoperative ischaemia [3–6]. The true incidence of postoperative ischaemia is difficult to ascertain because the usual associated symptoms and signs may be masked in the postoperative period by the residual effects of anaesthesia, opioid analgesics or surgical pain. Myocardial infarction in the postoperative period may occur without chest pain (21–60%) [3, 7] and may be diagnosed only by investigation of clinical events such as hypotension or retrospectively at postmortem. Previous studies of postoperative cardiac status have used discrete ECG recordings either in the early postoperative period or at 24-h intervals [3, 8]. This method cannot guarantee detection of significant transient ischaemia, which may occur at any time in response to stress such as pain, hypoxia, tachycardia or hypertension. The diagnosis of ischaemia, however, has been made easier by the development of more reliable ECG monitors using continuous computerized ST segment analysis [9].

The identification of factors present before operation which may identify the risk of postoperative myocardial infarction is important. The risk indices described by Goldman and co-workers [10] and Detsky and co-workers [11] have been used. However, Detsky suggested that factors in their populations may not apply elsewhere. Examples of these factors are recent myocardial infarction, cardiac failure or arrhythmias before surgery, but the relative contribution of these and other factors in patients in the U.K. is not well described.

In the present study, we have used continuous ECG monitoring with analysis of ST segment changes to detect the incidence of postoperative myocardial ischaemia in an at-risk group of patients, and any associated risk factors.

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TABLE I. *Patient characteristics and risk factors, and details of operations (number of patients in each category). HT = Treated hypertension; MI = previous myocardial infarct; GI = gastrointestinal; GU = genito-urinary.*

Patient characteristics			Details of operations		
Age: 45–86 yr			Surgery	GI	47
(mean 69.9, median 71 yr)				GU	51
Sex: 75 male; 33 female				Vascular	10
ASA rating	I	0			
	II	52	Duration of surgery (min)	< 30	21
	III	53		30–60	36
	IV	3		> 60	51
	V	0			
			Ventilation	Controlled	80
Goldman score	0–5	45		Spontaneous	28
	6–11	46			
	12–20	15	Anaesthetic	Halothane	12
	21+	2		Isoflurane	66
				Enflurane	18
Smoking (day^{-1})	None	82		Trichloroethylene	1
	1–5	14		Spinal	11
	6–10	1			
	11+	11	Preop. drugs	Diuretics	33
				Beta-blockers	28
Disease	HT	55		Ca^{2+} antagonists	22
	MI	56		Nitrates	12
	Angina	56			
	Other	7	Postop. oxygen duration (h)	1–4	48
				> 4	60

PATIENTS AND METHODS

Following Ethics Committee approval, we studied 108 patients undergoing non-cardiac surgery. All patients were older than 45 yr and known to have cardiovascular disease before operation. This included a history of angina, previous myocardial infarction (> 6 months before), cardiac failure, treated hypertension, valvular heart disease, or any combination of these conditions. Written informed consent was obtained from all patients.

Preoperative assessment included full medical history, physical examination and ECG. Factors of particular interest were age, sex, arterial pressure, smoking history, current drug therapy, Goldman score, ASA rating and the nature of the cardiovascular disease. Details of perioperative management were recorded subsequently; the factors of interest were the type and duration of surgery, anaesthetic regimen, all intraoperative and postoperative arterial pressure recordings, and duration of prescribed postoperative oxygen therapy (table I).

The "Compas" computerized ambulatory ECG surveillance system was used. This is a portable lightweight unit (about the size of a Sony "Walkman") which is attached to the patient via four chest electrodes. The monitor contains a microprocessor-based solid state system programmed with algorithms for accurate interpretation of the ECG. This is a fully automated system which detects, diagnoses and records ischaemic changes and arrhythmias as they occur. The data are stored in the unit for subsequent printing in a standardized report form. The time-correlated report is generated on downloading to a dedicated printer. The report consists of tables, graphs and selected ECG events, documenting arrhythmias, ST segment changes and heart rate. In the present study, the unit was programmed to an ST mode selecting augmented unipolar leads V2, V5 and AVF. The ST mode reports changes in the ST segment (relative to the baseline) lasting > 30 s and includes ST elevation > 2 mm, ST upsloping depression ≧ 2 mm, or ST horizontal or downsloping depression ≧ 1 mm. The times at which these changes start and end are recorded.

Each patient underwent continuous ECG monitoring. The monitor was attached to the patient on the day before surgery to obtain a preoperative recording of up to 24 h (mean duration 14.8 h). The unit was removed immediately before surgery and re-applied in the recovery room. Monitoring was then continued for a further 48 h, with a downloading of data at 24 and 48 h.

Data from the Compas monitor included records of all significant shifts of the ST segment and hourly count of ventricular ectopics. Ischaemic changes were analysed further as ischaemic events and ischaemic time. An ischaemic event was defined as an episode of ST segment depression of > 1 mm below, or elevation of > 2 mm above, the baseline, and persisting for 1 min or more (i.e. events reported in two or more consecutive minutes). The total number of events occurring in each 24-h period of monitoring was recorded, and averaged to give a unit of ischaemic events per hour. The number of these events associated with tachycardia (defined as an increase of 10 % or more from the resting baseline heart rate) was recorded. Ischaemic time was defined as the total duration of ischaemic events in each 24-h period, which was then averaged to give a unit of ischaemic time (min h^{-1}).

Ventricular ectopic activity was quantified by recording the maximum hourly count of ventricular ectopic beats (VEB) which occurred in each 24-h period (VEB h^{-1}). This method was chosen as our pilot studies had shown that VEB tended to occur in clusters over a few hours.

Statistics

Statistical analyses were performed using SPSS/PC+V2.0. Correlations were sought between ischaemic times, ischaemic events, VEB count and all of the proposed possible risk variables. Stepwise multiple regression analysis was then applied. Calculations of mean values and their comparison between groups were performed using analysis of variance and paired *t* test. The distribution of ischaemia and VEB within groups were compared using chi-square.

Patients were followed up by means of a postal questionnaire to their General Practitioners after 6 months and 1 year. Details of any deterioration in their cardiovascular status were requested.

RESULTS

Ischaemia

Before operation, 88 patients (81 %) had ischaemic changes on their ECG, and this number increased to 93 (86 %) after operation. Ischaemia was commoner in men both before ($P < 0.001$) and after operation ($P = 0.025$), and occurred more frequently after operation in those patients in whom it was present before operation ($P = 0.0029$). No patient complained of chest pain.

TABLE II. *Mean ischaemic times (min h^{-1}) expressed as mean, range and median. Patients are grouped according to presence or absence of hypertension (HT), angina or previous myocardial infarction (MI).* *P = *0.038 (paired* t *test)*; †P = *0.043 (ANOVA)*

	Before operation	After operation	
		Day 1	Day 2
All patients	10.7	13.4	14.7
(*n* = 108)	0–58	0–60	0–60
	2.4	1.8	3.9
HT	12*	17.1*†	17.8
(*n* = 55)	0–58	0–60	0–60
	2.4	2.7	4.5
No HT	9.6	9.6†	11.6
(*n* = 53)	0–58	0–60	0–60
	2.5	1.5	2.7
Angina	11	13	15.5
(*n* = 56)	0–58	0–60	0–60
	1.5	1.8	2.3
No angina	10.5	13.7	14
(*n* = 52)	0–58	0–60	0–60
	3.1	1.7	4.4
MI	10.9	13.5	15.5
(*n* = 56)	0–58	0–60	0–60
	1.3	2.4	4.3
No MI	10.5	13.3	13.9
(*n* = 52)	0–58	0–60	0–60
	3.1	1.1	3.4

The mean number of ischaemic events before operation was 4.6 h^{-1}, and of these 1.75 (38 %) were associated with tachycardia. After operation, the mean number of events was 4.48 h^{-1} and, of these, 2.73 (61 %) were associated with tachycardia. This difference between number of events associated with tachycardia before and after operation was significant ($P = 0.046$). There were no other significant differences in numbers of ischaemic events between the various risk groupings.

The mean values for ischaemic time for different disease groups are listed in table II. For all patients, the mean ischaemic time before operation was 10.7 min h^{-1}; it was 13.4 min h^{-1} on the first day after operation, and 14.7 min h^{-1} on the second day (ns). Patients with treated hypertension had a mean postoperative ischaemic time of 17.1 min h^{-1} on the first day after operation, and this was significantly different from both their preoperative ischaemic time of 12 min

h^{-1} ($P = 0.038$), and the postoperative time of 9.5 min h^{-1} in those patients without hypertension ($P = 0.043$). No other group showed significant changes in ischaemic time.

The ischaemic time after surgery had a positive correlation with preoperative time ($P < 0.001$), Goldman score ($P = 0.014$), the minimum recorded preoperative systolic arterial pressure ($P = 0.004$), maximum ($P = 0.002$) and minimum ($P = 0.004$) peroperative systolic arterial pressure and the presence of treated hypertension ($P = 0.02$). With stepwise multiple regression analysis, postoperative ischaemic time was found to correlate with preoperative ischaemic time ($P < 0.001$) and with the maximum recorded peroperative systolic arterial pressure ($P = 0.040$). The presence of preoperative treated hypertension did not achieve significance ($P = 0.12$), but in these patients the maximum recorded peroperative systolic arterial pressure was significantly greater (mean 153 mm Hg compared with 144 mm Hg for the non-hypertensive group) ($P = 0.045$).

After operation, myocardial infarction occurred in two patients. A 75-yr-old man, who had undergone oesophagogastrectomy, suffered fatal cardiac arrest on the third day after operation, just 6 h after Compas monitoring had been discontinued. Ischaemic times for this patient were shorter than mean times for all 3 days of monitoring (0.3 min h^{-1}, 1.35 min h^{-1} and 1.8 min h^{-1}, respectively). The second patient, a 72-yr-old man who had undergone bowel surgery, had an anterior myocardial infarction on the third day after operation, but survived and was still alive 6 months later. His preoperative ischaemic time was prolonged (57 min h^{-1}) but was reduced on both postoperative days (21.5 min h^{-1} and 31 min h^{-1}, respectively).

Ventricular ectopics

Before operation, 92 patients (85 %) had VEB, with a mean maximum rate of 62 VEB h^{-1}, and a median of 7 VEB h^{-1}. They occurred more frequently in men ($P = 0.002$). The greatest recorded rate in one patient was 1187 VEB h^{-1} (approximately 19 VEB min^{-1}), increasing to 1914 VEB h^{-1} after operation. The hourly rate had a positive correlation with Goldman score ($P = 0.037$) and diuretic therapy ($P = 0.037$).

After operation, 93 patients (85 %) had VEB; nine of these had had none before operation. The overall mean maximum rate was 109 VEB h^{-1}, significantly more than the preoperative rate of 62 VEB h^{-1} ($P = 0.027$). When analysed by disease grouping (table III), the postoperative rate was significantly greater than the preoperative rate in those patients without treated hypertension ($P = 0.029$). No other factor was associated with any significant change in the VEB rate. With multiple regression analysis, however, the postoperative rate was found to correlate positively with the preoperative rate ($P < 0.001$), diuretic therapy ($P < 0.001$) and the Goldman score ($P < 0.001$).

TABLE III. *Mean maximum ventricular ectopic beat (VEB) rate (VEB h^{-1}) expressed as mean, range, median. Patients are grouped according to the presence or absence of hypertension (HT), angina or previous myocardial infarction (MI).* *P = *0.027 (paired* t *test);* †P = *0.029 (paired* t *test)*

	Before op.	After op.
All patients ($n = 108$)	62* 0–1197 7	109* 0–1914 12
HT ($n = 55$)	74 0–1197 5	91 0–1362 7
No HT ($n = 53$)	50† 0–479 8	130† 0–1914 17
Angina ($n = 56$)	44 0–410 7	109 0–1914 12
No angina ($n = 52$)	81 0–1197 9	110 0–1362 12
MI ($n = 56$)	51 0–537 7	111 0–1914 11
No MI ($n = 52$)	74 0–1197 6	107 0–1362 13

Patient follow up

One year after surgery, six patients had been lost to follow up. Of the remaining 102, 15 had died. Three deaths were a result of myocardial infarction. The other deaths were caused by malignant disease (10), stroke (one) and head injury (one). Of the cardiac deaths, one occurred on the third day after operation, one at 2 months, and the third 8 months later.

Of the survivors, one patient had a myocardial infarction 48 h after operation but was alive and well 6 months later. Four other patients were on altered medication for worsening angina 6 months later, and two more after 12 months.

DISCUSSION

We studied 108 patients with known cardiovascular disease and therefore likely to be at risk from adverse cardiac events in the perioperative period. There was a high incidence of ischaemic events and ventricular arrhythmias. The duration of postoperative ischaemia correlated with that of preoperative ischaemia and peroperative systolic arterial pressure, and was increased significantly following surgery on patients with treated hypertension.

Ischaemic events occurred in 81% of our patients before operation, and this reflects our selection of an at-risk group. The rate was 18–40% in other studies using continuous ECG monitoring [12–14]. Some of these studies were based on patients about to have cardiac surgery, and as our criteria for an ischaemic event were similar, the greater incidence in our patients may be a reflection of differences in patient selection. The majority of preoperative events were not associated with tachycardia, and this agrees with previous observations that most perioperative ischaemic ECG changes occur without acute haemodynamic changes at their onset [14]. This is consistent with the concept that many transient ischaemic episodes may be related to intermittent decreases in myocardial oxygen supply rather than increased demand, resulting from increased coronary artery tone or platelet aggregation [15]. However, further stress to the myocardium is more likely to precipitate ischaemia, and this may explain the greater proportion of ischaemic events after operation which were associated with tachycardia.

Overall, anaesthesia and surgery did not worsen preoperative ischaemia significantly. Similar observations have been made in previous studies, involving patients undergoing coronary artery bypass grafting (CABG) [12], or non-cardiac surgery [13]. However, patients with treated hypertension, with or without other cardiovascular disease, became significantly more ischaemic after operation. Although these patients were receiving antihypertensive medication which was continued up to, and including, the day of surgery, their pre- and peroperative systolic arterial pressures were significantly greater than those of other patients. Although patients with untreated hypertension are generally accepted to be at increased risk of perioperative morbidity [16, 17], the widely used cardiac risk indices of Goldman and colleagues [10] and Detsky and colleagues [11] do not include moderate hypertension (diastolic arterial pressure < 110 mm Hg) as a significant risk factor. The data from our study suggest that, even though apparently adequately treated, patients with hypertension were at risk from higher peroperative arterial pressures and increased ischaemia after operation.

Significant correlations with postoperative ischaemic time were found for preoperative ischaemic time, the presence of treated hypertension, preoperative and peroperative systolic arterial pressure, and the Goldman score. Preoperative ischaemic time and the maximum recorded peroperative systolic arterial pressure remained the only significant independent correlates following multiple regression analysis. Thus there was no statistical association between postoperative ischaemic time and patient age, sex, ASA rating, smoking habits, angina, previous myocardial infarction, ventricular ectopics, type or duration of surgery and anaesthesia, preoperative drug therapy or duration of postoperative oxygen therapy. Historically, many of these features have been cited as significant risk factors in the occurrence of perioperative cardiac morbidity, although from a recent review [17] it is apparent that many previous studies have had conflicting results. The reviewer concluded that recent myocardial infarction and heart failure are the only proven preoperative predictors, and that intraoperative factors associated with increased risk appear to be emergency surgery, vascular surgery, prolonged thoracic or upper abdominal surgery, hypotension and tachycardia.

The relationship of perioperative ischaemia to cardiac outcome is not clear. Slogoff and Keats, in their study of 1023 patients undergoing CABG, found a correlation between postoperative myocardial infarction and perioperative ischaemia [18]: infarction was almost three times as frequent in patients with ischaemia. In a study of 176 patients undergoing elective vascular surgery, a positive correlation was found between preoperative ischaemia and postoperative cardiac events, defined as myocardial infarction, unstable angina or pulmonary oedema [19].

Of our patients who developed postoperative myocardial infarction, the one who died had very little ischaemia before infarction, while the survivor had high ischaemic times before and after operation. Of those whose cardiac status had deteriorated in the 12 months after surgery, there was no correlation with pre- or postoperative ischaemic times, or with any of the risk factors considered.

The development of ambulatory ECG monitors has shown that episodes of ST segment changes occur in patients with or without cardiovascular disease [20–22]. Such ECG changes may not always represent myocardial ischaemia in otherwise healthy patients, but probably do in those with coronary artery disease [21]. This is supported by studies using haemodynamic, radionuclide imaging and angiography methods [20, 22, 23]. In our study we found the Compas monitor to be safe, reliable and quite acceptable to the patients. It would have been useful to continue monitoring during induction of anaesthesia and surgery, but the possibility of damage to the monitor by diathermy prevented this.

The high incidence of VEB in our patients is not unusual. The prevalence of VEB within the normal population during a 24-h period of monitoring was reported to be between 17 and 100% in different studies [24], and appears to increase with age [25, 26]. It is also greater in males than females for any given age [27], and this was borne out in our results. Patients taking diuretics had more VEB than other patients after operation, and this may be related to changes in serum potassium concentration.

The significance of VEB is debatable. They are not uncommon in the normal population and are usually benign in the absence of heart disease. Frequent VEB in patients with evidence of ventricular dysfunction or with acute myocardial infarction are indicative of increased risk [28, 29]. Earlier studies have tried to define the predictive value of intraoperative arrhythmias. Steen, Tinker and Tarhan reported them as significant [30], whilst Rao, Jacobs and El-Etr found no correlation between incidence or type of arrhythmias and perioperative re-infarction [31]. Few studies have assessed adequately the importance of preoperative arrhythmias. They feature in Goldman's risk index as an independent predictor of cardiac complications, but in his study, patients who died did so for reasons other than the observed arrhythmia, and he considered them important as a marker of more severe heart disease [10]. In our patients we found no correlation between pre- or postoperative VEB rate and ischaemic times, or with final outcome.

We have demonstrated the high incidence of ischaemic ECG changes and ventricular arrhythmias occurring in the perioperative period in patients with cardiovascular disease. The frequency of VEB was significantly increased following surgery, but did not correlate with either ischaemic time or outcome. Anaesthesia and surgery increased significantly the ischaemic time in patients with treated hypertension. Postoperative ischaemic time may be related to peroperative systolic arterial pressures, which were greater in these patients.

If silent ischaemic ECG changes are an intermediate stage in the development of overt angina or myocardial infarction, this observation is important, suggesting that more meticulous control of peroperative arterial pressure could be beneficial. However, we failed to show a correlation between ischaemic time and cardiac mortality and morbidity, and this link has yet to be established.

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POSTOPERATIVE PROTEIN METABOLISM: EFFECT OF NURSING ELDERLY PATIENTS FOR 24 H AFTER ABDOMINAL SURGERY IN A THERMONEUTRAL ENVIRONMENT

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SUMMARY

We have studied the effect of intraoperative body heat conservation and 24-h thermoneutrality on postoperative whole body protein turnover using stable isotope methodology in a group of elderly patients undergoing colorectal surgery for recto–sigmoid adenocarcinoma. Two groups of eight patients were studied. One group (control, or cold) received routine intraoperative and post-operative care. All patients in the second group (warmed) were maintained at normothermia during anaesthesia and surgery; these patients were nursed after surgery in a warm room (ambient temperature 28–30 °C) for a period of 24 h. General anaesthesia, surgical care and nutritional support were similar in both groups. A constant nutritional intake, based on nitrogen 0.1 g kg^{-1} day^{-1} and energy 20 kcal kg^{-1} day^{-1}, was provided orally for 7 days before surgery and i.v. after operation for 4 consecutive days. Whole body protein breakdown and synthesis, as assessed by stable isotope methodology, increased significantly 2 and 4 days after surgery in both groups ($P < 0.01$), but the increase in protein breakdown in the warmed group on day 2 was significantly less than that in the cold group ($P < 0.05$). The increase in leucine oxidation in the warmed group on the 2nd day after surgery was not significant, and was less than the increase observed in the cold group ($P < 0.05$). However, by the 4th day, leucine oxidation was enhanced significantly in both groups ($P < 0.01$). The cumulative urinary nitrogen excretion over 4 days and the loss of fat-free mass, as measured by total body potassium 7 days after surgery, were significantly less in the warmed group compared with the cold group ($P < 0.05$). Urinary excretion of adrenaline and cortisol after surgery was significantly less in the warmed group compared with the cold group ($P < 0.05$). Thus the attenuated whole body protein breakdown and amino acid oxidation observed in the warmed group after surgery might be explained, to some extent, by the specific hormonal suppression achieved with thermoneutrality.

KEY WORDS

Metabolism protein. Temperature · cooling, metabolism.

Surgery is associated with changes in plasma and muscle contents of amino acids, resulting in loss of nitrogen from the body [1]. The conventional use of nitrogen balance as a criterion for assessing postoperative protein metabolism has a major limitation in that it provides no insight into the mechanisms of the processes involved [2]. Negative nitrogen balance might be the result of a decrease in protein synthesis while protein breakdown is unaffected, augmented proteolysis while synthesis remains unchanged, or intermediate permutations of these processes. In addition, nitrogen equilibrium does not necessarily reflect an adequate state of organ protein metabolism or of nutritional status, as it does not reveal possible alterations in the intensity, quality or distribution of tissue and organ protein metabolism [3].

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Recent advances in stable isotope methodology have now made it possible to provide a more direct determination of whole body protein turnover after surgery by measuring breakdown, oxidation and synthesis of body proteins [4].

The effect of maintenance of normothermia during and immediately after surgery on postoperative nitrogen economy and energy expenditure has been investigated in previous studies [5, 6] and shown to be beneficial in attenuating protein loss. Moreover, nursing patients with burns and major fractures at a thermoneutral temperature may attenuate post-injury increase in metabolic rate and urinary nitrogen excretion [7].

The present study was designed to evaluate the changes in whole body protein turnover, fat-free mass and catabolic hormones occurring during the first 4 days after colorectal surgery in patients maintained normothermic during anaesthesia and surgery, and nursed in a thermoneutral environment during the first 24 h after operation.

PATIENTS AND METHODS

We studied 16 patients suffering from well differentiated recto–sigmoid adenocarcinoma undergoing either anterior or abdomino–perineal resection. In all subjects, the tumour was localized and no metastatic dissemination was found by either ultrasound of the liver or by the surgeon. None of the patients suffered from malnutrition or metabolic disorders and all gave informed consent to participate in this investigation, which was approved by the local Ethics Committee.

A daily controlled oral diet containing nitrogen 0.1 g/kg body weight and 1200–1600 calories (5021–6698 kJ) (1.1 times the resting metabolic rate), as estimated from the equations of Harris and Benedict [8], was commenced 7 days before surgery under direct supervision of a dietician. The same amount of nitrogen and calories was administered i.v. after surgery, starting 6 h from the end of surgery when cardiorespiratory conditions were stable, and maintained for 4 days. This nutritional regimen, based on a mixture of glucose, lipids and amino acids (KabiVitrum, Stockholm) was administered via a peripheral cannula at a constant rate by means of a volumetric infusion pump (IMED 928, IMED, Milton). The caloric contribution was as follows: carbohydrate 35 %, fat 60 % and protein 5 %. On the day before surgery, skinfold thicknesses (biceps, triceps, subscapular and iliac crest) and mid-arm circumference were measured and the percentage body fat calculated [9]. In addition, total body potassium (TBK) was measured using a whole body counter and fat-free mass calculated [10].

Anaesthesia, surgery and postoperative care

Premedication comprised papaveretum 15–20 mg and hyoscine 0.2–0.4 mg i.m. 60–90 min before surgery. General anaesthesia was induced with thiopentone and neuromuscular block obtained with pancuronium. The lungs were ventilated to normocapnia with a mixture of 70 % nitrous oxide and enflurane in oxygen. Patients were allocated randomly to two groups (cold or warmed). The cold group ($n = 8$) served as controls, and these patients received routine anaesthetic and surgical care. At the end of surgery, they were kept in the recovery room for a period of 1–2 h before leaving for the ward, where they were nursed routinely. The ambient temperature in the wards varied between 19 and 23 °C during the period of investigation. In contrast, in the patients in the warmed group, core temperature was maintained during surgery at preoperative values by active warming of the inspired gases, i.v. fluids and skin surface. At the end of surgery all patients in this group were transferred for a period of 24 h to a thermostatically controlled room adjacent to the recovery area where the ambient temperature was maintained between 28 and 30 °C and relative humidity was between 30 and 40 %.

During surgery all patients in the two groups received an i.v. infusion of Hartmann's solution 6 ml kg^{-1} h^{-1}. Whole blood was administered when blood loss exceeded 20 % of the patient's circulating volume.

Anaesthesia and surgery occurred mid-morning and the operations were performed by the same surgical team. Pain relief after surgery consisted of a continuous subcutaneous infusion of papaveretum 3–7 mg h^{-1} for 72 h.

Before induction of anaesthesia, a thermocouple probe was inserted under direct vision in the aural canal and secured with cotton wool to avoid draughts. Aural canal temperature (an indication of core temperature) was measured before and at the end of surgery, and hourly for the first 24 h after surgery.

Ambient temperature in the thermostatically controlled room and the wards was measured in the proximity of the patient with a thermocouple probe. All the probes and the thermometer had

TABLE I. *Patient characteristics in the two groups studied (mean (SD or range)). BMI = Body mass index; FFM = fat-free mass*

	Cold group ($n = 8$)	Warmed group ($n = 8$)
Sex (M:F)	4:4	5:3
Age (yr)	70 (58–78)	73 (63–78)
Weight (kg)	63 (17)	65 (11)
BMI (kg m^{-2})	23 (2)	24 (4)
Fat (%)	28 (5)	26 (4)
FFM (kg)	43 (9)	49 (6)
Serum albumin (g $litre^{-1}$)	43.2 (2.4)	41.5 (7.1)

TABLE II. *Clinical data of the two groups studied (mean (SD))*

	Cold group ($n = 8$)	Warmed group ($n = 8$)
Postabsorptive period before surgery (h)	15 (3)	13 (4)
Duration of surgery (min)	191 (22)	182 (17)
Blood loss (ml)	875 (125)	927 (178)
Total amount of s.c. papaveretum administered over 24 h (mg)	127 (27)	108 (18)

been calibrated previously and found to be accurate to ±0.1 °C over the temperature range studied.

Experimental procedure

Oral and i.v. nutritional intakes were withheld from midnight before the morning of the studies, which were conducted between 08:00 and 12:00. The tracer infusions were carried out in all patients the day before surgery and on days 2 and 4 after surgery. A superficial vein in the dorsum of the hand was cannulated to provide access for infusion of L-[1-^{13}C]leucine. Blood was sampled from a cannula placed in the contralateral hand vein. L-[1-^{13}C]Leucine (99 %, ^{13}C) and 99 % ^{13}C-sodium bicarbonate ($NaH^{13}CO_3$) were purchased from Cambridge Isotope Laboratories (Cambridge, MA, U.S.A.).

Blood and air samples were collected before the infusion to measure basal carbon-13 enrichment, after which prime doses of $NaH^{13}CO_3$ 0.08 mg kg^{-1} and L-[1-^{13}C]leucine 0.5 mg kg^{-1} were administered. The continuous infusion of labelled leucine was started immediately and continued for a period of 4 h. Two hours after the start of the isotope infusion, when the tracer was assumed from previous studies to have reached an isotope steady state, venous blood and expired air samples were collected every 15 min for the remainder of the study. All blood samples were centrifuged immediately at 4 °C and the plasma was stored at −70 °C until required for analysis.

Plasma α-[^{13}C]ketoisocaproate (α-KIC) enrichment was determined by chemical ionization selected-ion monitoring mass spectrometry using n-ketovaleric acid as an internal standard [11]. Carbon-13 labelled carbon dioxide ($^{13}CO_2$) enrichment in expired breath was determined on the day of the study by means of isotope ratio mass spectrometry using an established technique [12]. Plateau enrichment for both plasma α-KIC and expired carbon dioxide was considered to have been established provided the coefficient of variation was less than 5 % at 2–4 h of the infusion.

Whole body leucine kinetics were calculated using a two-pool stochastic model applied during the steady state conditions obtained during the final 2 h of each study [13]. Plasma enrichment of α-[^{13}C]KIC was used as the basis for calculating both flux and oxidation of leucine [14]. In the calculation of oxidation, a factor of 0.81 was used to account for the fraction of $^{13}CO_2$ released from leucine but retained in the bicarbonate pool of the body.

Indirect calorimetry was performed over a 1-h period during the 2-h isotope plateau on each day of the study, and oxygen consumption ($\dot{V}o_2$) and carbon dioxide production ($\dot{V}co_2$) were measured (Datex, Deltatrac, Finland).

TBK was measured non-invasively on the day before and 7 days after surgery in a whole body counter with a precision of 3 % and accuracy of 4 % [10]. The method relies on the measurement of gamma emissions from naturally radioactive potassium (potassium-40) present in the body as 0.012 % of the naturally occurring isotopes of potassium. As 98 % of potassium is located in the lean tissue, this measurement represents an index of fat-free mass. The degree of preoperative depletion, an indicator of nutritional assessment, was calculated from the ratio between the predicted and measured preoperative values, while the change in TBK occurring with surgery was obtained from the difference between the preoperative and postoperative measured TBK concentrations.

Twenty-four hour urine collections were obtained on two consecutive days before surgery and four consecutive days after surgery and analysed for total nitrogen, creatinine, noradrenaline, ad-

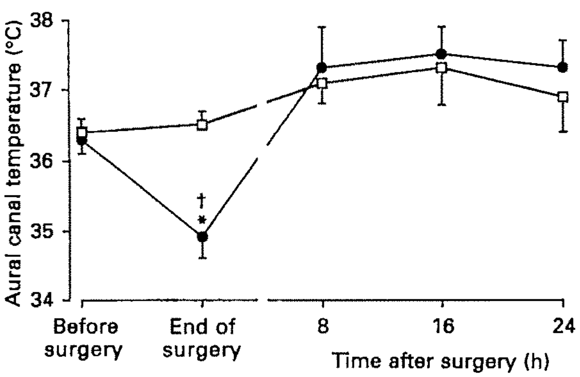

FIG. 1. Mean values (SD) of aural canal temperature during and after surgery in the cold (●) and warmed (□) groups. Significant differences: *between values for preoperative and end surgery in the cold group ($P < 0.05$); †between values for cold and warmed groups ($P < 0.05$).

renaline and cortisol concentrations. Total nitrogen was measured by the automated method of chemiluminescence [15] and creatinine determined by the SMAC automated procedure. Urinary catecholamine concentrations were measured by reversed-phase ion-paired high pressure liquid chromatography with electrochemical detection [16], and urinary cortisol was measured by a fluorimetric method [17].

Statistical analysis

Results are expressed as mean (1 SD). Paired and unpaired Student's *t* test were used when appropriate, and differences for all tests were considered significant at $P < 0.05$.

RESULTS

There were no significant differences between the two groups in patient characteristics, duration of surgery or blood loss (tables I, II). Aural canal temperature in the cold group decreased significantly ($P < 0.01$) during surgery and returned towards preoperative values during the first 8 h of recovery (fig. 1). The peak temperature was recorded in both groups 16 h from the end of surgery. Shivering was recorded only during the first 2 h after operation in four of eight patients in the cold group.

Urinary total nitrogen and creatinine

Preoperative mean (SD) values of urinary total nitrogen were similar for both groups: nitrogen 1.01 (0.02) mmol kg^{-1} day^{-1} per mmol of creatinine for the cold group and 0.97 (0.02) mmol kg^{-1} day^{-1} for the warmed group. Cumulative excretion of nitrogen during the first 4 days after operation was significantly greater in the cold group compared with the warmed group: nitrogen 5.5 (1.0) mmol kg^{-1} day^{-1} per mmol of creatinine for the cold group and 4.1 (1.2) mmol kg^{-1} day^{-1} for the warmed group ($P < 0.05$). Creatinine excretion increased significantly from 6.6 (3.1) mmol day^{-1} in the cold group and 5.9 (2.7) mmol day^{-1} in the warmed group before surgery to 13.8 (5.7) mmol day^{-1} and 14.6 (6.3) mmol day^{-1}, respectively, on day 1 after surgery. Thereafter, the values decreased in both groups, but remained greater than preoperative values during the study period. No difference was observed between the two groups.

Whole body protein turnover

The sequential changes in whole body leucine kinetics following surgery in the two groups are presented in figure 2. In the fasted state, flux was equal to breakdown, there being no contribution from exogenous sources of leucine. Carbon-13 enrichments for plasma α-KIC and expired carbon dioxide had an average coefficient of variation of 4.37% and 0.92%, respectively.

Leucine flux/breakdown increased significantly in both groups, 2 and 4 days after surgery; however, the greatest increase occurred in the cold group (28%) on day 2, and this was significantly different from that occurring in the warmed group (18%) ($P < 0.04$). On the fourth day after surgery there was no significant difference between the two groups. In the cold group, leucine oxidation increased significantly by 24% ($P < 0.001$) on day 2 and remained increased on day 4 ($P < 0.001$). In contrast, no significant increase occurred on day 2 in the warmed group, but on day 4 leucine oxidation was significantly increased compared with preoperative values ($P < 0.01$). Incorporation of leucine into protein (protein synthetic rate) increased significantly in both groups on both days 2 and 4 ($P < 0.01$), and no difference was observed between the two groups at any time.

Total body potassium

The mean (SD) preoperative percentage ratio of observed over expected value of TBK was similar in both groups of patients studied: 0.97 (0.1) in the cold group and 0.98 (0.07) in the warmed group. The mean (SD) decrease in TBK 7 days

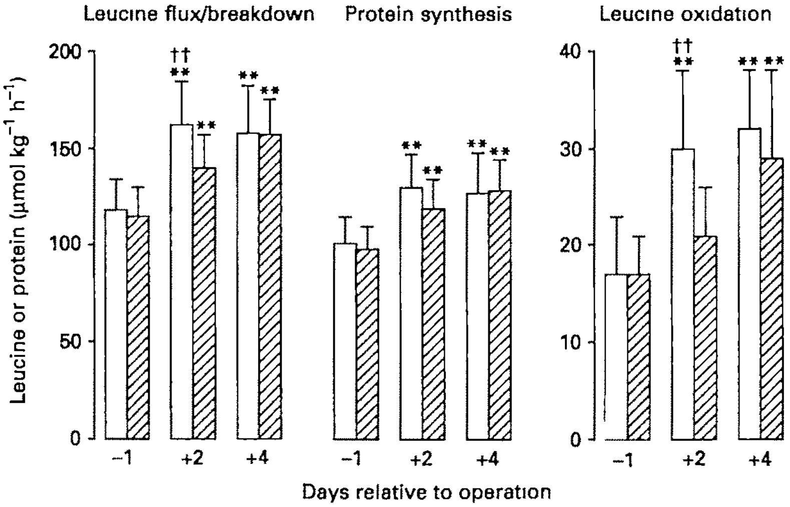

FIG. 2. Mean values (SD) of whole body protein breakdown, synthesis and oxidation before and after surgery in the cold (□) and warmed (▨) groups. Significant differences between: **values for preoperative and postoperative periods in both groups ($P < 0.01$); ††values for cold and warmed groups ($P < 0.01$).

TABLE III. *Mean* (SD) *urinary concentrations of adrenaline and cortisol in the two groups studied.* *$P < 0.05$ *compared with cold group*

	Before surgery	After surgery			
		Day 1	Day 2	Day 3	Day 4
Adrenaline (µmol day^{-1})					
Cold group	0.05	0.57	0.32	0.16	0.18
($n = 8$)	(0.05)	(0.50)	(0.38)	(0.14)	(0.15)
Warmed group	0.02	0.12*	0.25	0.08	0.10
($n = 8$)	(0.01)	(0.11)	(0.35)	(0.03)	(0.04)
Cortisol (nmol day^{-1})					
Cold group	458	4000	2058	2797	1911
($n = 8$)	(140)	(965)	(872)	(1479)	(1287)
Warmed group	330	1554*	1091*	1047*	1715
($n = 8$)	(90)	(496)	(665)	(467)	(993)

after surgery was 342 (162) mmol in the cold group and 183 (95) mmol in the warmed group ($P = 0.03$).

Urinary adrenaline, noradrenaline and cortisol

The changes in urinary excretion of adrenaline and cortisol are presented in table III. Adrenaline excretion was similar in both groups before surgery and increased significantly after surgery in both groups ($P < 0.05$). Adrenaline concentration, however, was significantly greater in the cold group compared with the warmed group on day 1 ($P < 0.05$). Thereafter, the excretion in the warmed group remained lower, but it was not significantly different from the cold group. Urinary excretion of cortisol increased significantly after surgery in both groups, but this was significantly less in the warmed group compared with the cold group on days 1, 2 and 3 ($P < 0.05$). Urinary noradrenaline increased significantly after surgery in both groups and there was no significant difference between them.

Gas exchange

$\dot{V}O_2$ and $\dot{V}CO_2$ increased in both groups on days 2 and 4 after surgery by approximately 7–10%. No significant difference was observed between the two groups at any time.

DISCUSSION

This study has shown that conservation of body heat during surgery and preservation of thermoneutrality extended for 24 h after surgery caused a significantly smaller increase in whole body protein breakdown and amino acid oxidation during the postoperative period. This resulted in attenuated excretion of body nitrogen and loss of fat-free mass.

We have reported that attempts to prevent loss of body heat during surgery resulted in attenuation of protein breakdown as measured by urinary total nitrogen and 3-methylhistidine excretion [18]. However, as we highlighted previously, control of dietary intake during metabolic studies is essential for interpretation of changes in protein metabolism with surgery [19]. Nutrient withdrawal reduces protein synthesis by up to 40 % [20], while refeeding a malnourished patient causes stimulation of synthesis [21]. In the present study we have approached this problem by standardizing the nutritional intake before and after surgery; thus the nitrogen intake was moderate and the calories were based on the patients' resting energy expenditure. This strict dietary control allowed us to separate the effect of trauma from that of starvation in the interpretation of the changes in protein turnover [19].

None of the patients was nutritionally depleted before surgery, as indicated both by physical characteristics and plasma concentrations of albumin.

The particular surgical procedure was chosen as it represents a reproducible model of major intensity of trauma which elicits neuroendocrine responses and substrate changes in the postoperative period. Attempts to quantitate the possible effects of a malignant tumour on protein metabolism of the host have produced conflicting results. Thus the first such study in humans reported enhanced protein turnover in patients with colorectal neoplasm which was approximately proportional to the estimated tumour burden [22]. Similar results have been obtained in patients with various tumours [23–25] in adults with non-oat cell carcinoma of the lung [26] and in children with leukaemia and lymphoma [27]. In sharp contrast to these observations, resection of colonic tumours failed to show any effect on protein metabolism [28]. Similarly, no effect of a tumour on host protein metabolism could be demonstrated in cachectic patients with lung tumours [29], germ cell tumours [30] or in patients with malignant tumours of the large bowel, with or without metastatic disease [31]. That the apparent discrepancies outlined above may result from differences in experimental design, patients, feeding regimens or methods of data presentation have been examined in detail [31].

As observed in this study, whole body protein breakdown (measured by leucine kinetics) increased significantly in both groups, 2 and 4 days after surgery. However, the breakdown was significantly less enhanced in the warmed group on day 2 compared with the cold group. This result was supported by the fact that the rate of oxidation of leucine on day 2, in those patients maintained at thermoneutrality for the first 24 h after surgery, did not change significantly from preoperative values. Rates of protein breakdown and oxidation between the two groups were not statistically different by day 4.

Whole body protein synthetic rate increased significantly in both groups after surgery by approximately the same amount, indicating similar availability of amino acids for the formation of new proteins in the body. This was associated with an increase in postoperative oxygen consumption on days 2 and 4 in the same direction, reflecting the energy-requiring nature of the processes most likely to be involved: protein synthesis and gluconeogenesis.

It is of interest that the attenuation in whole body protein breakdown and oxidation in the warmed group was limited to the 2nd day after operation, which coincided with the provision of thermoneutrality during the first 24 h after surgery. These results are in agreement with previous work on the effect of high ambient temperature on postoperative protein breakdown in surgical patients [32]. It is at this same period that the excretion of urinary adrenaline and cortisol was significantly less in the warmed group compared with the cold group. A role for these counter-regulatory hormones in modulating protein metabolism has been proposed previously [33]. However, other mediators of proteolysis occurring in plasma after trauma might be involved [34].

This is the first evidence we have that hormonal modulation might be a mechanism for reduced protein breakdown and oxidation in association with maintenance of thermoneutrality. From the present results, one could speculate that provision of thermoneutrality extended for a longer period of time might spare some postoperative protein breakdown and amino acid oxidation throughout the catabolic phase. In contrast, whole body protein synthesis was not enhanced by preservation of body heat.

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VIABILITY AND DISTRIBUTION OF BACTERIA AFTER PASSAGE THROUGH A CIRCLE ANAESTHETIC SYSTEM

P. M. MURPHY, R. B. FITZGEORGE AND R. F. BARRETT

SUMMARY

We have assessed in vitro *the viability of eight species of micro-organism suspended as aerosols and passed through a soda-lime absorber rebreathing system. As had been predicted, the soda-lime exerted a potent cidal effect on non-sporing organisms, all of which were rendered non-viable. One percent of the spore bearing organism,* Bacillus subtilis, *was still viable after 30 min contact. Although* Bacillus subtilis *is an organism of low pathogenicity, spores may be more resistant to the alkaline medium of the soda-lime. The micro-organisms were observed to lodge in all components of the breathing system, with the greatest concentration being recovered from the corrugated tubing. We recommend that disposable components of the circle breathing system should be changed, and the non-disposable parts sterilized or disinfected, daily. Soda-lime cannisters should be sterilized or disinfected when changing the soda-lime.*

KEY WORDS

Equipment · absorbers, circle system. Infection

Carbon dioxide absorption was introduced into clinical anaesthesia by a dentist, Alfred Coleman [1, 2], and Brian Sword first described the use of the circle absorber system in 1930 [3]. Incorporation of the circle absorber into closed and semi-closed breathing systems allows a reduction in the amount of volatile agent and gases required, and helps to control pollution of the theatre environment.

A disadvantage of the system, however, is the potential for the circulation and retention of infective organisms. We have investigated the retention of eight micro-organisms passed through a Medishield Mk4a carbon dioxide absorber (fig. 1) and the viability of these micro-organisms in Ohmeda Medisorb soda-lime. We chose the eight micro-organisms on the basis of their widespread distribution in the environment, presence as upper respiratory tract commensals or opportunistic pathogenic ability. We have investi-

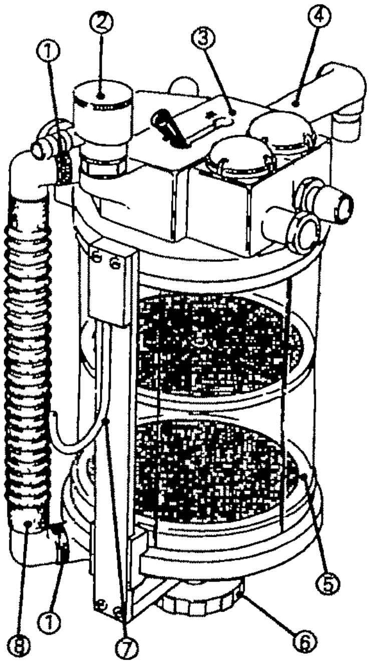

FIG. 1. The Medishield Mk4a carbon dioxide absorber. 1 = Hose connections; 2 = antipollution valve; 3 = head assembly; 4 = rebreathing bag elbow; 5 = canister; 6 = clamp screw; 7 = support hook; 8 = corrugated hose.

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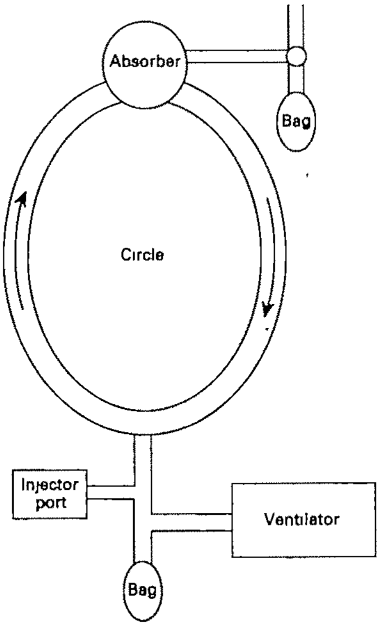

FIG. 2. Diagram of system used to assess lodgement of micro-organisms on components of the carbon dioxide absorber and associated apparatus.

TABLE I. *Survival of organisms exposed to soda-lime*

Organism	Count without soda-lime	Count after contact with soda-lime	
		10 min	30 min
Klebsiella pneumoniae NCTC NOC 9633-10	1×10^5 ml^{-1}	—	—
Candida albicans NCTC NCPF 3153	7×10^4 ml^{-1}	—	—
Bacillus subtilis NCTC NC 10073-03	1.2×10^5 ml^{-1}	3.1×10^4	1.5×10^3
Staphylococcus aureus NCTC NCO 4163-12	3.8×10^6 ml^{-1}	—	—
Pseudomonas aeruginosa NCTC NCO 6749-14	1.7×10^4 ml^{-1}	—	—
Serratia marcescens NCTC 10211-08	1.1×10^5 ml^{-1}	—	—
Escherichia coli NCTC NCO 8196-12	1.9×10^5 ml^{-1}	—	—
Streptococcus pneumoniae NCTC 7465	1×10^5 ml^{-1}	—	—

gated also the lodgement of micro-organisms in components of the soda-lime canister and other parts of the circle rebreathing system.

In an unpublished pilot study by two of the authors (P.M.M. and R.F.B.), wet and dry bacterial swabs were taken and cultured from the inspiratory and expiratory valves of the Mk4a absorber, at the beginning and end of 40 consecutive elective, clean cases. In each case the anaesthetic consisted of oxygen, nitrous oxide and either enflurane or isoflurane, with a fresh gas flow of 1 litre min^{-1} in a spontaneously breathing patient. No growth occurred from these samples.

METHODS

Organisms

Eight species of micro-organism, including one spore-forming organism, were resuscitated on blood agar plates from National Collection of Type Culture (Colindale) freeze-dried cultures. After overnight growth at 37 °C, the organisms were suspended in a nutrient broth and standardized by total counts made on a Helber slide examined under dark-ground microscopy.

Bactericidal action of soda-lime

The micro-organisms were suspended in 10 ml of nutrient broth and assayed for viability before addition of soda-lime 1 g. The suspensions were shaken at room temperature and assumed a pH of 11.0 within 2 min of the addition of the soda-lime. Viability was reassessed at 10 and 30 min.

Retention of infectious organisms in the Medishield Mk4a carbon dioxide absorber

Infectious aerosols were generated either in a Collison spray which gave particles of < 5 µm in diameter, or in a Devilbiss ultrasonic aerosol generator which gave particles of approximately 10 µm in diameter. To examine the retention of micro-organisms in the carbon dioxide absorber, aerosols of the organisms were prepared and passed through the absorber for 1 min in air at a flow rate of 10 litre min^{-1}. In the first pass the absorber was empty and in the second pass it was filled with Medisorb soda-lime. The aerosols were collected from the expiratory port of the absorber in a Porton-type impinger containing nutrient broth 10 ml, together with an anti-foam agent (polyethylene glycol 2000). The collected fluid was assayed for viable organisms by the colony counts seen on blood agar plates.

Lodgement of micro-organisms on components of the carbon dioxide absorber and associated apparatus

To examine the possibility that micro-organisms may lodge and possibly be disseminated on the inlet and outlet valves of the carbon dioxide

TABLE II. *Effect of passing infectious aerosols through a container of soda-lime, at 10 litre* min^{-1}. *Aerosols produced in Collison spray (< 5 µm diameter) except for †produced in Devilbiss generator (10 µm). Aerosols were collected for 1 min in nutrient broth in Porton impinger*

Organism aerosol (< 5 µm diameter)	Before passing through soda-lime	After passing through soda-lime	Not retained (%)
Klebsiella pneumoniae	2.2×10^4 ml^{-1}	2×10^3 ml^{-1}	9
Candida albicans	1×10^4 ml^{-1}	2×10^3 ml^{-1}	20
Bacillus subtilis	6×10^4 ml^{-1}	3×10^3 ml^{-1}	5
Staphylococcus aureus	3×10^4 ml^{-1}	1.2×10^4 ml^{-1}	40
Pseudomonas aeruginosa	5×10^4 ml^{-1}	8×10^3 ml^{-1}	16
Escherichia coli	5×10^4 ml^{-1}	9×10^3 ml^{-1}	18
Streptococcus pneumoniae	3×10^4 ml^{-1}	7.5×10^3 ml^{-1}	25
Serratia marcescens	4×10^4 ml^{-1}	8×10^3 ml^{-1}	20
†	5×10^4 ml^{-1}	5×10^3 ml^{-1}	10

absorber and associated components (including the corrugated tubing and the reservoir bag), the apparatus was coupled to an East Radcliffe ventilator. This was used to drive the circuit via a T-piece, the other limb of which was connected to a 1-litre reservoir bag acting as a compliant lung. Distal to this T-piece, an injector port was connected into the circuit from the aerosol pump (fig. 2). Using the Devilbiss ultrasonic aerosol generator an aerosol containing *Serratia marcescens* was injected via this port at a flow rate of 10 litre min^{-1} for 5 min. After this time the components of the circuit, including the absorber, were removed and examined for viable organisms. Valve diaphragms were shaken in 20 ml of nutrient broth and the reservoir bags and tubing were washed out with 50 ml. The samples were assayed for viable organisms by colony counts on blood agar plates.

RESULTS

Survival of organisms exposed to soda-lime

Of the eight species of micro-organism, seven were rendered non-viable within 10 min of exposure. However, a little more than 1 % of *Bacillus subtilis* remained viable at 30 min (table I).

Retention of micro-organisms in the carbon dioxide absorber

Between 5 and 40 % of the test set of organisms in aerosol of particle size < 5 µm were not retained by passage through the carbon dioxide absorber (table II). Increasing the particle size in relation to one species (*Serratia marcescens*) improved retention only marginally.

TABLE III. *Lodgement of organisms on components of carbon dioxide absorber and breathing system. (50 litre of* Serratia marcescens *aerosol when collected in an impinger over a period of 5 min without being passed through the apparatus contained* 2×10^6 *viable organisms)*

Component	No. of organisms associated with component	Organisms retained (% of total)
Tubing	2.4×10^5	12
Inspiratory valve	8.8×10^2	0.044
Expiratory valve	3.2×10^2	0.016
Reservoir bag (CO_2 Absorber)	2.3×10^4	1.15
Reservoir bag (Ventilator)	3.1×10^4	1.55
	Total retained:	14.76

Lodgement of organisms on components of the carbon dioxide absorber and associated apparatus

All components examined trapped micro-organisms (table III). Most (12 %) were found in the corrugated tubing connecting the carbon dioxide absorber with the ventilator. A significant number of organisms (approximately 1 %) were recovered from the reservoir bag. Inlet and outlet valve membranes trapped 0.044 % and 0.016 %, respectively.

DISCUSSION

Ventilators [4] and humidifiers [5] are known to be contaminated easily with organisms and therefore appropriate filters and sterilization policies are applied. Previous reports have implicated anaesthetic equipment in the genesis of respiratory tract infections [6–11], but many are inconclusive and fail to provide bacteriological proof of causation [12]. Others dispute that the circle breathing system acts as a significant source of infection or is likely to be instrumental in causing pulmonary complications after operation [13–15]. The use of bacterial filters and sterile circuits for each anaesthetic does not alter the incidence of postoperative pulmonary infections [12, 16].

Two previous studies have investigated the ability of micro-organisms to pass through a soda-lime canister. Adriani and Rovenstine [17] were unable to demonstrate passage of *Bacillus coli* and *Mycobacterium tuberculosis* through a soda-lime canister. Dryden [18] demonstrated that *Pseudomonas aeruginosa* and *P. mirabilis* remained viable after passing through a Waters canister packed with soda-lime, but did not quantify the percentage of organisms that passed. He also reported that both these organisms were killed when placed in contact with an aqueous suspension of soda-lime. However, the latter failed to kill *M. tuberculosis* after prolonged contact.

A cross-section of commonly occurring organisms was used in our study. *Klebsiella pneumoniae*, *Serratia marcescens* and *Pseudomonas aeruginosa* are common hospital-acquired organisms colonizing the respiratory tract and may cause respiratory infections, particularly in the immunocompromised patient [19]. *Streptococcus pneumoniae* is a common nasopharyngeal commensal and a frequent respiratory pathogen in both primary and secondary infections [19]. *Staphylococcus aureus* is a commensal in the nasopharynx in 10–30 % of the normal population [20], and *Candida albicans* is part of the normal mouth flora; both these organisms can cause significant opportunistic infections. Surgery is associated with alterations in cell-mediated and humoral immunity [21, 22] and this may be accentuated by the clinical status of the patient and any concurrent medications [23], thereby increasing the patient's susceptibility to infection.

In the first part of our study we confirmed that soda-lime exerts a potent cidal effect on seven common, non-sporing organisms, all of which were rapidly rendered non-viable. One per cent of the spore-bearing organism examined, *Bacillus subtilis*, was still viable after 30 min contact. *Bacillus subtilis* is a widespread organism of low pathogenicity found in soil, dust and air; spores may be more resistant to the highly alkaline medium than the parent organism. However, the survival of spores may not pose a hazard [24]. The potency of the bactericidal effect of soda-lime is presumably a result of the presence of the highly alkaline calcium, sodium and potassium hydroxides. Under clinical conditions, the reaction of these hydroxides with carbon dioxide in the presence of water results in the formation of carbonates. The heat released by this exothermic reaction results in a temperature of up to 60 °C inside the canister, further discouraging the survival of any micro-organisms present. Du Moulin [25] has reviewed the unfavourable environmental conditions that affect the viability of micro-organisms in the circle system. The effects of temperature [26] and humidity changes [27], droplet evaporation [28] and inspired oxygen may all be detrimental to micro-organism viability.

For the soda-lime to exert a cidal effect, impaction of the organism with the granules is required. In the second part of our study, we have shown that impaction of organisms under the conditions of our experiment was unreliable: 5–40 % of the organisms were not retained by the soda-lime in the canister. Soda-lime for use in anaesthesia is prepared in a highly porous, granular form to produce a large surface area for maximum efficiency [29], as the primary reaction takes place only on the surface of the granules. The controlled range of granule sizes minimizes gas channelling and facilitates good filling during packing. Optimum mesh size provides minimum resistance to breathing and sufficient surface area for efficient carbon dioxide absorption. Although smaller diameter soda-lime granules would improve impaction of organisms and increase the surface area for absorption, the unfavourable effect on airway resistance makes it unacceptable.

In the third part of our study, organisms were observed to lodge in all components of the breathing system model. The highest concentration of organisms was recovered from the flexible tubing, the structure of which makes it particularly prone to retention of organisms. Smooth-bore tubing would be preferable in this respect. Valve diaphragms made of a suitable lightweight plastic material could replace the laminated mica discs which fracture easily at their edge and offer foci on which organisms can lodge.

Policies on sterilization and disposal of components of breathing systems vary. Disinfection removes or kills the majority or all of infective organisms. Sterilization is required, in addition, to kill spores. However the latter technique is more likely to damage equipment. Although we agree with the conclusion of previous workers [13–15, 17] that it is unlikely that cross infection may occur between successive patients using the same circle breathing system, failure to cleanse regularly and sterilize the apparatus should not be condoned [30]. We advocate continuation of a formal policy for sterilization or disinfection of non-disposable components, and change of disposable components of the circle breathing system. All tubing and reservoir bags should be sterilized or disinfected daily, or changed, if disposable. Inspiratory and expiratory valves should also be sterilized daily. Soda-lime canisters should be sterilized at the time of each change of soda-lime load.

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COMPARISON OF TWO METHODS FOR PREDICTING DIFFICULT INTUBATION†

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SUMMARY

Two methods of predicting difficult laryngoscopy were compared prospectively. Mallampati class and Wilson risk-sum were determined before operation and laryngeal view graded in 675 patients. Both tests identified five of 12 difficult laryngoscopies; twice as many patients were predicted to be difficult by Mallampati classification than by Wilson risk-sum. Inter-observer variation was minimal using Wilson risk-sum, but considerable for Mallampati classification. We prefer the Wilson risk-sum for assessment of the airway, while noting that both tests have poor sensitivities.

KEY WORDS

Complications: difficult intubation. Intubation, tracheal: preoperative assessment.

The unexpected difficult intubation is a major concern for the anaesthetist. Recently, several different methods of predicting possible difficulty in intubation have been devised [1]. Two of the most interesting are those of Mallampati and co-workers [2] and Wilson and colleagues [3]. The Mallampati test classifies the view of pharyngeal structures with the mouth wide open and the tongue protruded. It is a simple test and may be performed quickly. The Wilson test is more complex and assesses five factors, including weight and head and neck mobility.

The purpose of this study was to compare the Mallampati classification with Wilson risk-sum in the prediction of difficult laryngoscopy, and to assess inter-observer variation in performing these tests.

PATIENTS AND METHODS

In a prospective study, 751 patients (448 female) requiring tracheal intubation were seen before operation by one of four observers—three registrars and one senior registrar (training grades). Sex, age and weight of each patient were recorded. All patients were assessed for Mallampati class and Wilson risk-sum.

Mallampati classification was performed as described originally by asking the patient to protrude the tongue maximally while in the sitting position [2]. In class 1, faucial pillars, soft palate and uvula are visible. In class 2, faucial pillars and soft palate may be seen, but the uvula is masked by the base of the tongue. In class 3, only the soft palate is visible. The manoeuvre was repeated to ensure maximum visibility of the pharyngeal structures.

Wilson risk-sum was then ascertained. This scores five factors (weight, head and neck movement, jaw movement, receding mandible and buck teeth) from 0 to 2, giving a total ranging from 0 to 10 [3].

Anaesthetists of all grades, who were not informed of the preoperative Mallampati class and Wilson risk-sum, assessed difficulty of laryngoscopy at intubation. Laryngoscopy was graded on a scale of 1–5 as described by Wilson and colleagues [3]: grade 1 = almost all of cords visible; grade 2 = only half of cords visible; grade 3 = only arytenoids visible; grade 4 = only

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TABLE I. *Wilson risk-sum values (0–5) and laryngoscopy grades (1–5) in 677 patients*

Wilson risk-sum	Laryngeal view 1	2	3	4	5
0	388	70	11	5	1
1	104	35	6	0	1
2	26	13	1	1	0
3	4	3	2	3	0
4	1	0	0	0	1
5	1	0	0	0	0

TABLE II. *Mallampati class (1–3) and laryngoscopy grades (1–5) in 675 patients*

Mallampati class	Laryngeal view 1	2	3	4	5
1	398	84	17	5	1
2	49	4	2	1	0
3	76	33	0	3	2

epiglottis visible; grade 5 = not even epiglottis visible. Difficult laryngoscopy was defined as grades 4 and 5—that is, no more than the epiglottis could be seen.

TABLE III. *Sensitivity, specificity and positive predictive value (PPV) for Wilson risk-sum and Mallampati classification in 675 patients assessed by one of four observers and in 543 patients for whom data from observer four are excluded. A Wilson risk-sum of 2 or more, or Mallampati class 3 are predictors, and laryngoscopy grades 4 or 5 are diagnosis, of difficult laryngoscopy*

	Wilson	Mallampati
All observers (675 patients)		
Sensitivity	0.42	0.42
Specificity	0.92	0.84
PPV (%)	8.9	4.4
Observers 1–3 (543 patients)		
Sensitivity	0.40	0.50
Specificity	0.95	0.92
PPV (%)	13.3	10.0

Sensitivity, specificity and positive predictive value were calculated for each test. Sensitivity is the proportion of difficult laryngoscopies which were predicted to be difficult. Specificity is the proportion of straightforward laryngoscopies which were predicted to be easy. Positive predictive value is the proportion of patients predicted to be difficult who proved to be difficult [4].

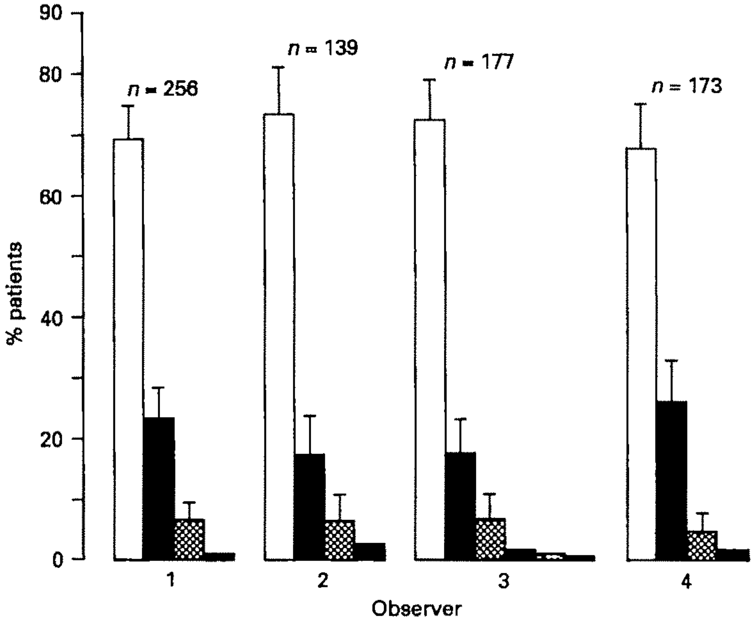

FIG. 1. Distribution of scores for Wilson risk-sum by observers 1–4 (95% confidence intervals). *n* = Number of patients observed. Risk-sums: □ = 0; ▨ = 1; ⊠ = 2; ▧ = 3; ⊡ = 4; ■ = 5.

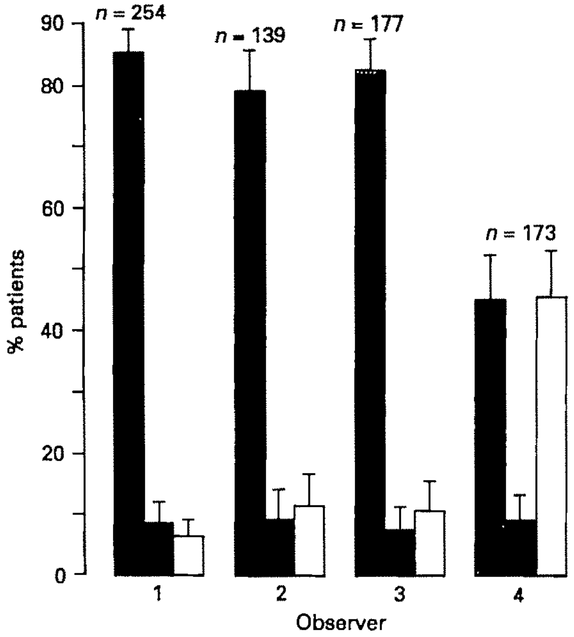

FIG. 2. Distribution of scores for Mallampati class by observers 1–4 (95% confidence intervals). *n* = Number of patients observed. Mallampati class: ▨ = 1; ■ = 2; □ = 3.

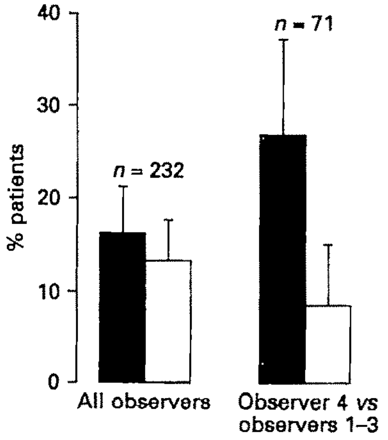

FIG. 3. Percentage (95% CI) of patients, assessed by two observers, for whom the observers disagreed over scoring difficult or easy laryngoscopy for Mallampati classification (▨) and Wilson risk-sum (□). Left: all observers. Right: Observer 4 *vs* observers 1–3. *n* = Number of patients observed.

Scores for Mallampati class and Wilson risk-sum were examined to assess the distribution of scores assigned by each observer. In addition, 232 patients were assessed before operation by two of the observers independently, so that a direct between-observer comparison of scoring could be made.

Ninety-five percent confidence intervals (95% CI) were calculated where appropriate.

RESULTS

Complete data were available for 675 of 751 patients. Patient age ranged from 16 to 87 yr (mean 46.6 yr). Weight ranged from 30 to 133 kg (mean 65.1 kg); 38 patients weighed 90 kg or more and one patient weighed more than 110 kg.

Tables I and II show Wilson risk-sum and Mallampati class, respectively, for each grade of laryngoscopy. Twelve patients were graded 4 or 5 at laryngoscopy, giving an incidence of difficult laryngoscopy of 1.8% (95% CI 0.77–2.75). Of these 12 patients, five had a Wilson risk-sum of 2 or more and five were Mallampati class 3. Sensitivities, specificities and positive predictive values for the two tests are shown in Table III.

Figures 1 and 2 show scoring of Wilson risk-sum and Mallampati class, respectively, by each observer. For all four observers, approximately 70% of patients had a Wilson risk-sum of zero while 30% had a risk-sum of one or more. Observers one, two and three classified over 75% of patients Mallampati 1, whereas observer four classified 45% of patients Mallampati 1 and 46% Mallampati 3.

For the 232 patients in whom pairs of the observers predicted, independently, straightforward or difficult laryngoscopy, we examined the number of occasions when the pair of observers agreed or disagreed in their predictions (fig. 3). There was no significant difference in the number of agreements and disagreements between the two observers when the data for all observers are used. However, when observer four was compared with the other observers, there were significantly more disagreements as to prediction of difficulty for the Mallampati classification compared with Wilson risk-sum.

Excluding the data for observer four, there remained 543 patients, of whom nine were found to be laryngoscopy grade 4 or 5. Sensitivities, specificities and positive predictive values for the two tests in these patients are shown in table III.

Seventy-three patients had restricted head and neck movement and seven of these scored two points on Wilson criteria (head and neck movement less than 90°). Three patients with restricted head and neck movement presented difficulty at laryngoscopy; one was Mallampati class 1 and two were class 3.

DISCUSSION

The incidence of difficult laryngoscopy in this study was 1.8%. This agrees with the 1–3% quoted in previous work [5]. Wilson and colleagues [3] found an incidence of 1.5% using the same criteria for difficult laryngoscopy as this study. In contrast, Mallampati and co-workers [2] gave an incidence of 13%. Their definition of difficult laryngoscopy, however, included grade 3 laryngoscopy. The incidence was 4.3% if grade 3 laryngoscopy is excluded.

Examining the data for all four observers in our study, a Wilson risk-sum of 2 or more correctly predicted only five of the 12 difficult laryngoscopies. For a similar incidence of difficult laryngoscopy, Wilson and colleagues predicted nine of 12 difficult laryngoscopies. The positive predictive values were the same (8.9%).

Comparison with the work of Mallampati and co-workers requires clarification because of the different criteria used. In their study, class 3 predicted 14 of the 28 patients having grade 3 or 4 laryngoscopy ("inadequate exposure of the glottis"). Re-examining their data with class 3 as a predictor and taking grade 4 ("glottis including corniculate cartilages could not be exposed") to define difficult laryngoscopy, five of nine difficult laryngoscopies were predicted correctly. Positive predictive value was 33%. We were able to predict correctly only five of 12, with a positive predictive value of 4.4%.

In our study, using the data for all four observers, sensitivities for Wilson risk-sum and Mallampati classification were the same (0.42). Positive predictive value for Wilson risk-sum was double that for Mallampati classification (8.9% and 4.4%, respectively). This implies that to detect the same proportion of difficult laryngoscopies, twice as many patients were predicted to be difficult using the Mallampati classification as the Wilson risk-sum. However, our estimates of positive predictive values were based on small numbers, with consequent wide confidence intervals.

Observer four classified a significantly greater proportion of patients Mallampati class 3 than the other observers (fig. 2). This was confirmed by examining the number of times pairs of observers agreed or disagreed in predicting difficult laryngoscopy (fig. 3). There was a significantly greater proportion of disagreement between observers when observer four was one of the pair. Our findings on inter-observer variation in using the Mallampati classification support those of Wilson and John [6].

After discussion with observer four, we feel that the likely explanation of this is that full patient co-operation was not obtained. A critical factor in achieving a reliable score for Mallampati classification is ensuring that the patient opens the mouth and protrudes the tongue maximally. Failure to apply this rigorously is a major pitfall when performing the assessment. In addition, Mallampati class may be affected if the patient inadvertently phonates during the assessment [7]. We found that Wilson risk-sum and Mallampati classification were similar in their predictive value when the data for observer four were excluded.

Concern has been expressed that the Mallampati classification may not discriminate those patients in whom difficult laryngoscopy is caused by limited head and neck mobility [8, 9]. Mallampati and co-workers identified four patients with moderately restricted mobility of the neck [2]. Two of these had "inadequate glottic exposure". The Mallampati classifications of these patients were not specified. In our study, of the three patients who had limited head and neck movement and who presented difficulty at laryngoscopy, two were Mallampati class 3. In view of the small number, we remain guarded about the validity of the classification in such patients.

The initial study by Wilson and colleagues [3] found that weight was the least useful of the five predictive factors. In the study by Mallampati and co-workers [2], the four patients weighing 130 kg or more had adequate glottic exposure. We found that, in removing weight from the risk-sum, the sensitivity was unchanged at 0.42 and positive predictive value improved to 10.9%. This suggests that the weight component of the Wilson risk-sum might be unnecessary. Of the 38 patients who scored points for weight, however, only one patient scored 2 points (that is, weight more than 110 kg). We are cautious about extending our findings to patients weighing more than 110 kg and further investigation is required in this group.

Failure to intubate the trachea and maintain oxygenation remains a significant cause of perioperative death associated with anaesthesia. This has been shown repeatedly in studies of anaesthetic mortality. *The Report of a Confidential Enquiry into Perioperative Deaths* found that of the three deaths attributable wholly to anaesthesia, one was caused by inability to intubate the trachea [10]. Similarly, the *Report on Maternal and Perinatal Deaths in Scotland 1981–1985* identified one of the three deaths directly caused by anaesthesia as being a result of failure to achieve tracheal intubation [11].

We were unable to predict more than 50% of the difficult laryngoscopies. This is of particular importance to the relatively inexperienced anaesthetist presented with a patient at risk of regurgitation. Increasing the sensitivity of the test by lowering its threshold, however, also increases the proportion of false positives. For example, in our study if, instead of a Wilson risk-sum of 2 or more, a risk-sum of 1 or more was taken as a predictor of difficult laryngoscopy, 50% of difficult cases were identified, but the false positive rate increased from 0.08 to 0.29. Of the patients who were predicted to be difficult, only 3% proved to be difficult. This has obvious implications for the provision of senior anaesthetic cover, and deserves wider discussion.

In conclusion, we were unable to reproduce the results of the original studies. We found that the sensitivities of Wilson risk-sum and Mallampati classification were similar, but poor. At best it was possible to identify only 50% of the difficult laryngoscopies, with a high false positive rate. In view of the significant inter-observer variation in performing the Mallampati classification, we prefer the Wilson risk-sum in airway assessment.

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PLASMA CONCENTRATIONS OF BUPIVACAINE FOLLOWING COMBINED SCIATIC AND FEMORAL 3 IN 1 NERVE BLOCKS IN OPEN KNEE SURGERY

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SUMMARY

We administered combined femoral 3 in 1 and sciatic nerve blocks to provide postoperative pain relief in 22 consecutive patients undergoing elective knee replacement surgery under spinal anaesthesia. The patients were allocated randomly to two groups. In group A (n = 11) the blocks were performed with 0.5% bupivacaine (with adrenaline) 3 mg/kg body weight and in group B (n = 11) 0.5% plain bupivacaine in the same dose was used. Serial plasma concentrations of bupivacaine were measured for up to 2 h and the duration of postoperative analgesia was measured in both groups. No significant differences were found between the two groups. There were no clinical signs or symptoms of bupivacaine toxicity in each group. This study demonstrated that, after combined sciatic and 3 in 1 femoral block, concentrations of bupivacaine associated with toxicity were not reached, even though the dose of bupivacaine administered exceeded the manufacturer's recommended dose by 50%.

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques sciatic and femoral 3 in 1 nerve blocks

In our experience, satisfactory postoperative analgesia following open knee surgery may be achieved using single 3 in 1 femoral and sciatic nerve blocks with 0.5% bupivacaine 3 mg/kg body weight with or without 1:200000 adrenaline. This dose exceeds that of 2 mg kg^{-1} recommended by the manufacturer, but is less than the 10 mg kg^{-1} used by Moore [1] in a similar study.

Recommended doses of local anaesthetic drugs depend upon variability of systemic absorption rates which are influenced by such factors as tissue perfusion and the likelihood of inadvertent i.v. injection. Smith [2, 3] showed that peak plasma concentrations of local anaesthetic drugs were greater following perineal and intercostal infiltration than after caudal and extradural injection with the same dose of drug.

Sciatic and femoral 3 in 1 nerve blocks appear to be associated with low rates of absorption. Therefore we have examined bupivacaine concentrations following combined sciatic and femoral 3 in 1 block with either plain 0.5% bupivacaine or 0.5% bupivacaine with adrenaline and related these to the bupivacaine concentrations associated with toxicity. We also recorded the incidence of adverse affects and the duration of analgesia.

PATIENTS AND METHODS

Following Ethics Committee approval, informed consent was obtained from 22 consecutive ASA I–III patients undergoing elective knee replacement surgery. The selected patients did not suffer any known sensitivity to local anaesthetics, have groin or lumbar sepsis, or have any contraindication to lumbar puncture.

Anaesthetic procedure

No premedication was given to the patient. On admission to the anaesthetic room, the patients were allocated randomly to one of two groups. The patient was re-identified and two 14-gauge i.v. cannulae were inserted under local anaesthetic (1% lignocaine). One cannula was used only for

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blood sampling. Dextrose saline was infused i.v. via the other cannula at a rate of 100 ml h^{-1}. ECG and non-invasive arterial pressure were monitored from the start of the procedure.

Spinal anaesthesia was performed with the patient in the sitting position using plain 0.5% bupivacaine 3 ml. Five minutes after the spinal block had been performed, the sciatic and femoral 3 in 1 nerve blocks were administered for postoperative pain relief. Group A received 0.5% bupivacaine with adrenaline 1:200000 and group B received plain 0.5% bupivacaine for the peripheral nerve blocks. The nerve blocks were performed with the aid of an insulated 22-gauge, 100-mm pole needle attached to a peripheral nerve stimulator (Neurostim: Hugosachs Elektronik Type 220).

The sciatic nerve block was performed using a classical posterior approach in all except five patients (three in group A and two in group B) who had undergone previous hip replacement; in these the anterior approach was used to avoid repositioning an anaesthetized patient with a possible prejudicial effect on the hip prosthesis. The femoral 3 in 1 nerve block was performed as described by Winnie [4]. The total volume of local anaesthetic (3 mg kg^{-1}) was distributed between the sciatic and femoral nerves in a ratio of 1:1.5.

Blood samples

Ten-millilitre blood samples were obtained in lithium heparin bottles. The plasma was separated within 4 h and stored at −20 °C until required for analysis. Samples were taken at the time of insertion of the i.v. cannula ($t = 0$), every 5 min after the peripheral nerve block for the first 30 min and every 15 min thereafter for the next 90 min.

Plasma concentrations of bupivacaine were measured using high pressure liquid chromatography, using the technique described by Wieland and Chou [5].

Patient assessment

The time taken for return of sensation to the blocked limb (lateral part of thigh for femoral 3 in 1 and plantar surface of foot for sciatic) was noted. The extent of analgesia to pinprick was assessed at 60-min intervals by a trained nurse observer who was blind to patient grouping, and the occurrence of adverse side effects was noted. The time of the patient's first request for analgesia for pain in the vicinity of the operation was noted.

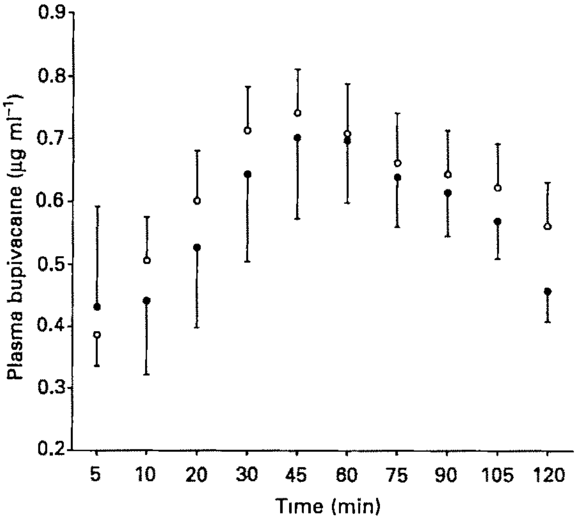

FIG. 1. Mean plasma concentration of bupivacaine up to 2 h after nerve blocks in group A (●, bupivacaine with adrenaline 1:200000) and group B (○, plain bupivacaine).

Statistics

Data were analysed using Student's *t* test for unpaired data and analysis of variance with repeated measures. $P < 0.05$ was taken as significant. Data are shown in the text as mean (SEM).

RESULTS

There were no significant differences between the two groups in age and weight. Anaesthesia was uneventful in all patients and there was no evidence of a toxic reaction to the local anaesthetic. The peripheral nerve blocks were successful in all 22 patients. Two patients, however, needed analgesia only 6 h after completion of the operation.

The mean peak plasma concentration of bupivacaine using the plain 0.5% solution was 0.703 (0.09) μg ml^{-1} and that for the combination of bupivacaine with adrenaline was 0.787 (0.14) μg ml^{-1} (ns; $t = 0.4$, $P = 0.6$). The mean time to peak plasma concentration of bupivacaine was 60 (7) min in the group receiving plain 0.5% bupivacaine (group B) and 63 (7) min in group A ($P > 0.05$). The bupivacaine concentration–time profiles for the two groups did not differ significantly (analysis of variance with repeated measures: $F = 0.11$, $P = 0.7$) (fig. 1).

The time taken for return of sensation was 9 (1) h in group A and 14 (3) h in group B for the femoral distribution and 13 (1) h in group A and

20 (4) h in group B for the sciatic distribution. However, some patients experienced pain at the site of surgery before complete return of sensation in the representative areas tested. The mean time to first analgesia was 15 (2) h in group A and 20 (4) h in group B. The difference was not significant ($t = -1.08$, $P = 0.29$). No patient reported any untoward effects following the peripheral nerve blocks.

DISCUSSION

This study has demonstrated that, after combined sciatic and 3 in 1 femoral block, concentrations of bupivacaine associated with toxicity (> 2 μg ml^{-1}) were not reached, even though the dose of bupivacaine administered exceeded the manufacturer's recommended dose (2 mg kg^{-1}) by 50%.

The addition of adrenaline to bupivacaine did not influence significantly the peak plasma concentrations of bupivacaine, time to reach peak concentration, or duration of postoperative analgesia. There were no concentrations in excess of the reported toxic concentration of 2 μg ml^{-1}. However, in one patient (weight 87.5 kg) who received bupivacaine with adrenaline for his nerve blocks, the peak plasma concentration of bupivacaine was 2 μg ml^{-1} at 5 min. He did not receive any sedation and exhibited no clinical signs or symptoms of toxicity. The duration of analgesia at the operation site for this patient was 12 h.

Time to first analgesia in both groups of patients was about 17 h. This included five patients who received opioids for pain at a site other than the operated knee, as patients undergoing knee replacement surgery frequently have a polyarticular affliction.

The potential toxicity of local anaesthetic drugs is determined by several factors which include site of injection [6, 7], rate of injection [8], concentration of drug used and the use of vasoconstrictors to reduce systemic absorption [9, 10].

One of the most importance factors contributing to the toxicity of local anaesthetic agents is the vascularity of the area into which they are injected [6, 11]. In this study, the time to peak concentration of bupivacaine in both groups was relatively slow (63 min in group A and 60 min in group B).

Reynolds [12] infused bupivacaine i.v. and described toxic symptoms of a minor nature at an arterial concentration of 1.5–2 μg ml^{-1}. Jorfeldt and colleagues [13] infused bupivacaine i.v. to a mean arterial concentration of 2 μg ml^{-1} with no neurological or cardiovascular side effects. They suggested that, in man, "the dangerous level" was 4 μg ml^{-1}. This value is supported by blood concentrations in patients during convulsions [14]. Toxicity is related, not to the total drug, but to the concentration of the drug which is free and active in the plasma. Bupivacaine has been shown to be highly protein bound, with 90% binding *in vivo* at concentrations of up to 5 μg ml^{-1} [15].

Although the concentration of bupivacaine was less at 120 min than the peak concentration in all patients, there is a possibility of later increases in the plasma concentration of bupivacaine if top up doses are administered through a catheter in the vicinity of the sciatic and femoral nerves, with the concurrent possibility of side effects.

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COMPARISON OF FOUR SUBARACHNOID SOLUTIONS IN A NEEDLE-THROUGH-NEEDLE TECHNIQUE FOR ELECTIVE CAESAREAN SECTION

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SUMMARY

We have used both spinal and extradural anaesthesia with a 26-gauge, long spinal needle through a 16-gauge Tuohy needle for elective Caesarean section. Four different subarachnoid solutions of bupivacaine were compared: 0.5% heavy bupivacaine alone, or with adrenaline, fentanyl or adrenaline and fentanyl. The incidence of complications and time of regression of the sensory block were analysed. The technique is recommended because it allows rapid onset of anaesthesia and the advantages of an extradural catheter. The subarachnoid solution of choice was 0.5% heavy bupivacaine 12.5 mg with fentanyl 10 µg

KEY WORDS

Anaesthesia: obstetric, Caesarean section Anaesthetic techniques: extradural, spinal. Anaesthetics, local. bupivacaine.

Extradural anaesthesia for Caesarean section has several advantages. It allows mothers to partake in the birth, decreases the stress response of surgery [1] and decreases postoperative requirement for analgesia. Patients experience less morbidity and mortality in comparison with those who have had a general anaesthetic [2]. Its intrinsic disadvantages are a failure rate (requirement for additional analgesia in 20% of patients [3]) and a time to onset of a full T4 block of at least 30 min [4] in patients in whom incremental techniques are used.

Subarachnoid anaesthesia offers similar advantages, with greater muscle relaxation [5], more rapid onset [6], no missed segments [6], minimal risk of drug toxicity [6] and better surgical anaesthesia [7]. For these reasons, it has been proposed as the anaesthetic method of choice for urgent Caesarean delivery [8]. Disadvantages include less control of block height [9], more rapid with a higher risk of hypotension [10], failure rate, non-continuous analgesia, and post-spinal headaches [11].

Some disadvantages of both these conduction anaesthetic techniques may be reduced by combining them. Subarachnoid injection may be made through a long, 26-gauge spinal needle introduced through an extradurally placed Tuohy needle before insertion of an extradural catheter [5, 12].

Using this method, we have compared four different subarachnoid solutions containing bupivacaine to ascertain if improved intra- and postoperative pain relief could be achieved. Adrenaline has been used because of its possible antinociceptive effect on the spinal cord [13] and improvement in quality of anaesthesia [14], and fentanyl because opioids appear to potentiate the antinociceptive effect of local anaesthetics [15].

PATIENTS AND METHODS

We studied 48 consecutive, healthy patients undergoing elective Caesarean section. Informed consent was obtained from all patients and the study was approved by the hospital Ethics Committee. The patients were allocated randomly to receive one of four subarachnoid solutions. All anaesthetics were given by four anaesthetists in training. Patient assessment was carried out by

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TABLE I. *Solutions used in the subarachnoid technique*

Group	0.5% Heavy bupivacaine (mg)	Fentanyl (µg)	Adrenaline (µg)	Saline (ml)
A	12.5	0	0	0.5
B	12.5	0	30	0.2
C	12.5	10	0	0.4
D	12.5	10	30	0.1

two observers who were blind to the solutions, which were prepared freshly by an anaesthetist not involved in the study.

Each patient was premedicated with oral ranitidine 150 mg the night before surgery, and ranitidine 150 mg with metoclopramide 10 mg orally 90 min before operation. A 16-gauge i.v. cannula was inserted and Hartmann's solution 1500 ml administered i.v. Monitoring of ECG, non-invasive arterial pressure and pulse oximetry was performed throughout the procedure. Intermittent fetal auscultation was performed until the start of surgery. The patients breathed oxygen 4 litre min^{-1} via a face mask until the baby was delivered.

All patients were placed in the left lateral position. Using a midline approach at the L3–4 interspace, a 16-gauge Tuohy needle with a Huber point was introduced into the extradural space. No accidental dural puncture was noted. Through the extradural needle was threaded a 12-cm, 26-gauge spinal needle with a Quincke point with the bevel parallel to the dural fibres [16]. Free flow of cerebrospinal fluid (CSF) occurred within an average of 12 s. Patients were then allocated randomly to receive 0.5% hyperbaric bupivacaine 2.5 ml (group A) alone or with adrenaline 0.3 mg (group B), fentanyl 10 µg (group C) or adrenaline 0.3 mg and fentanyl 10 µg (group D). All solutions were made up to a final volume of 3 ml with saline (table I). The spinal injection was made over a period of 45 s and when the injection was completed, the spinal needle was removed and an extradural catheter inserted so that 3 cm remained in the extradural space. No injection was made through the catheter at this time. The patient was turned supine with a 15° right lateral tilt and a wedge placed under the left hip. Hypotension (defined as a 20% decrease in mean arterial pressure or a systolic arterial pressure < 100 mm Hg) was avoided by administration of ephedrine infusion (ephedrine 30 mg in Hartmann's solution 500 ml). If hypotension occurred despite this prophylaxis, it was treated with increments of ephedrine 5 mg by i.v. bolus administration. The following observations were noted (all timings were from completion of the subarachnoid injection): time to T4 sensory anaesthesia to ethyl chloride spray; height of sensory block every 5 min for 30 min; incidence of nausea and vomiting. If this was unrelated to hypotension it was treated with i.v. droperidol 1.25 mg. Any complaint of somnolence or pruritus was noted by direct questioning.

Neonatal Apgar scores and samples of umbilical cord blood for blood-gas analysis were taken by the attending midwife.

Following the procedure the mother was asked to score her discomfort during the procedure using a 0–100 mm visual analogue scale. As an attempted prophylaxis against post-subarachnoid headache, 0.9% saline 30 ml was infused through the extradural catheter at the end of the operation [17].

Time to first request for analgesia was noted and 2% lignocaine 3 ml with adrenaline 15 µg was injected through the extradural catheter to exclude an intravascular or intrathecal position [9]. Ten minutes after this test dose, 0.25% plain bupivacaine 10 ml was injected. This was followed by preservative-free morphine 4 mg in normal saline 10 ml. The time to next request for analgesia was taken from the patient's notes. Pain was assessed using linear analogue pain scores (0 = no pain, 10 = maximum pain). Respiratory depression (defined as a ventilatory frequency < 10 b.p.m.) was observed by hourly monitoring of the ventilatory frequency for the first 24 h. The incidence of pruritus was ascertained by direct questioning. At 24 and 72 h, patients were questioned for maternal satisfaction, neurological problems and spinal headache.

Statistical analysis was performed using an analysis of variance (ANOVA) for parametric data, any statistically significant difference among the four groups was analysed by an unpaired two-tail t test. A chi-square test for non-parametric categorical data and a Mann–Whitney U test for non-parametric ordinal data were used. $P < 0.05$ was regarded as statistically significant.

RESULTS

There were no significant differences between groups in age, weight, height, gestation, parity, duration of surgery or neonatal condition at delivery (table II). Subarachnoid block charac-

TABLE II. *Patient characteristics (mean* (SD) *or [range])*

	Group A ($n = 12$)	Group B ($n = 12$)	Group C ($n = 12$)	Group D ($n = 12$)
Age (yr)	34.3 [18–39]	33.2 [22–41]	31.5 [23–36]	34 1 [20–37]
Weight (kg)	77.4 (10.5)	78 (5.0)	74.9 (11.4)	75.3 (14.6)
Height (cm)	166 (7)	167 (8)	163 (7)	160 (6)
Gestation (weeks)	38 (1)	38 (2)	38 (1)	38 (2)
Range	[37–39]	[32–41]	[37–39]	[35–40]
Nulliparous	3	3	5	4
Duration of surgery (min)	59 (8)	66 (18)	72 (23)	63 (11)

TABLE III. *Subarachnoid block characteristics (mean* (SD)). *$P < 0.006$; *** $P < 0.001$; *unpaired two-tailed t test for differences between groups*

	Group A	Group B	Group C	Group D
Time to T4 block (min)	7 9 (3 4)	5.7 (2.2)	6.1 (1.8)	5.8 (2.2)
Max height of block to cold (range)	C3–T3	C2–T2	C3–T2	C3–T2
Periop. pain scores (No. with VAS = 0)	6/11	6/11	11/11	12/12
Regression time to T10 (min)	130 (21)	149 (16)	150 (24)	187 (33)*
Time to analgesia request (min)	145 (26)	161 (18)	201 (29)***	229 (34)***

TABLE IV. *Complications of the subarachnoid anaesthetic.* *$P = 0.033$; *chi-square analysis of association between nausea and adrenaline*

	Group A	Group B	Group C	Group D
T1 block to cold	3/11	4/11	4/11	5/12
Hypotension	2/11	4/11	2/11	3/12
Nausea	3/11	7/11*	0/11	8/12*
Sleepiness	3/11	3/11	2/11	4/12
Pruritus	0	0	0	1/12

teristics are shown in table III. There was no significant association between the height of the subarachnoid block and patient height, weight or age. It was possible to commence surgery within 10 min of the subarachnoid injection in 46 of the 48 patients. There were two "failed" spinals. There was no significant difference of time to T4 sensory loss; all blocks reached their maximum height by 20 min; none had started to regress by 30 min. There was no relationship between maximum height of block and time to regress to T10. Addition of fentanyl or adrenaline singly had minimal effect on regression time of the subarachnoid block. The combination of adrenaline and fentanyl (group D), however, was associated with prolongation of block compared with groups A, B and C ($P < 0.01$). The addition of fentanyl (group C) or fentanyl and adrenaline (group D) resulted in a period of prolonged postoperative analgesia, compared with groups A and B ($P < 0.01$).

There were a large number of high blocks (16/45) reaching above the T1 level, but no differences between the groups (table IV). Two patients with high cervical blocks complained of a stuffy nose. There were no patients with blocks below T4. Hypotension occurred equally in all four groups, with an overall incidence of 24%. Of the 11 women who developed hypotension, eight required additional vasopressor treatment with ephedrine (6 mg i.v. on average). There was no association between block height and hypotension. Sleepiness occurred in 12 women and was distributed evenly among the four groups. There was a statistically significant relationship between sleepiness and height of block ($P < 0.001$). Nausea occurred in 18 patients (40%). I.v. droperidol was required in nine patients. There was a significant association between the incidence of nausea and the groups receiving adrenaline ($P = 0.033$). No patient in the bupivicaine–fentanyl group was nauseated.

TABLE V. *Pain relief with extradural morphine (mean* (SD) *and* [*range*])

	Group A	Group B	Group C	Group D
Time (min)	890 (437) [240–1440]	769 (468) [360–1440]	655 (465) [120–1440]	978 (502) [120–1440]
Pruritus	1/11	2/11	3/11	2/12

No patient had a pain score during the operation of > 17 mm, and none required additional analgesia or sedation. All the patients receiving fentanyl (groups C and D) had perioperative pain scores of zero (table III).

After operation there were no differences between groups for duration of analgesia provided by extradural morphine or in the incidence of pruritus (table V). One patient required treatment with naloxone 0.4 mg i.v. for pruritus.

One patient developed post-spinal headache which required an extradural blood-patch at 48 h. Forty-five mothers scored their satisfaction as "excellent" immediately after operation, at 24 h and at 72 h. No patient developed any neurological symptoms.

Three patients were excluded from analysis. One patient had a prolonged procedure (because of bleeding fibroids); two patients had failed subarachnoid block. No patient exhibited any sign of respiratory depression either during or after operation. We were unable to ascertain the existence of urinary retention because all the patients had indwelling urinary catheters for the first 24 h.

DISCUSSION

All anaesthetics were performed by four anaesthetists in training who had not used this technique before but were experienced in extradural blocks.

There were two "failed spinals", despite the free flow of CSF. This is a failure rate of 4%, which is comparable to those described by Moir [4] and Manchikanti [18].

There were a large number of high blocks (33% above T1), comparable to the results of Russell [19], but none of the patients in whom this occurred complained of ventilatory difficulties. There was no relationship with the incidence of hypotension, but the majority of these patients did complain of drowsiness. The addition of fentanyl 10 µg was not associated with sleepiness. The high level of sensory anaesthesia may relate to our method of assessment (loss of cold sensation to ethyl chloride spray), as loss of temperature discrimination may occur up to six segments above surgical anaesthesia [20]. In all our patients, however, there was bilateral surgical anaesthesia to pin-prick at T4.

In our study, 10 of 45 patients had a pain score for the operation greater than zero, but no patient required additional analgesia during the operation. This contrasts with other studies [5, 21–23] in which up to 50% of patients required i.v. opioids during operation. This is probably attributable in part to the smaller dose of bupivacaine (average 9 mg) used in these studies. All patients given subarachnoid fentanyl (groups C and D) had intraoperative pain scores of zero, similar to the findings of other workers [15, 23].

Groups C and D had a longer time until first request for analgesia, but there was no difference between them. It appears that the combination of opioid with local anaesthetic is synergistic. This has been shown for the combination of bupivacaine and morphine [21]. In a retrospective analysis of postoperative pain relief, McQuay found that patients given both opioid and regional block, before surgery, had a prolonged time to first request for analgesia [24]. It is now generally accepted that adrenaline has minimal effect in prolonging surgical anaesthesia, and group B had no prolongation of anaesthesia compared with groups A and C.

None of the solutions used resulted in a marked lack of side effects, although the bupivacaine–fentanyl solution had no incidence of nausea and vomiting. This has been observed elsewhere for extradural fentanyl during Caesarean section [25] and is in contrast with the adrenaline-containing solutions.

The use of extradural morphine gave excellent prolonged postoperative analgesia in over 30% of patients, with no requirement for additional opioid analgesia. Twenty per cent of subjects complained of pruritus; one of them required naloxone treatment. The analgesia obtained, however, compares poorly with comparable studies [26]. Four patients obtained less than 4 h analgesia, and there was marked variation in duration of analgesia.

All the patients expressed satisfaction with the anaesthetic. Several who had undergone previous Caesarean section under extradural anaesthesia remarked on the better quality of anaesthesia with this technique.

In conclusion, we feel that the combined needle-through-needle technique for Caesarean section is useful in that it provides the advantages of both subarachnoid block and the continuity of extradural analgesia. We recommend the use of bupivacaine with fentanyl as it offers some benefits: minimal nausea, good intraoperative and prolonged postoperative analgesia, and a low incidence of complications. The problem of hypotension following subarachnoid anaesthesia remains the greatest disadvantage; this requires careful monitoring and anticipation to avoid its adverse consequences.

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UTEROPLACENTAL AND FETAL HAEMODYNAMICS DURING EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION

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SUMMARY

We have studied the effects of extradural anaesthesia with bupivacaine (plain) in eight healthy parturients undergoing elective Caesarean section, on blood flow in maternal uterine and placental arcuate arteries and in fetal umbilical, renal and middle cerebral arteries, using a colour Doppler technique. Simultaneously, fetal myocardial function was investigated by M-mode echocardiography. Maternal and fetal blood velocity waveform indices did not change significantly. We found no changes in fetal myocardial function with extradural anaesthesia, except for an increase in the right ventricular inner end-diastolic dimensions. These results suggest that extradural anaesthesia has no detrimental effects on uteroplacental and fetal circulations in the uncomplicated pregnancy when maternal hypotension is avoided with rapid prehydration.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: extradural. Measurement techniques: Doppler ultrasonics, echocardiography. Placenta. blood flow velocity. Uterus: blood flow.

During the past few years, several studies have been performed using the Doppler technique for assessing haemodynamic changes, in both the pregnant woman and the fetus, which are associated with extradural block for Caesarean section. According to Robson and colleagues [1] no maternal cardiac or peripheral haemodynamic changes were found after induction of extradural anaesthesia when maternal systolic arterial pressure was maintained with a fluid preload. Studies on the effects of extradural block on maternal uterine and fetal umbilical artery blood flow velocity waveforms have demonstrated either no change in indices [2–4] or a decrease in resistance [5]. In contrast, Baumann and others [6] suggested an increase in resistance in uteroplacental circulation with an impairment in perfusion. The stability of the fetal circulation during extradural anaesthesia was attested by normal Apgar scores and umbilical pH or blood-gas values in all these studies.

The purpose of the present investigation was to evaluate the influence of extradural block for elective Caesarean section simultaneously on several maternal and fetal haemodynamic variables (vascular resistance in maternal uterine and placental arcuate artery, fetal umbilical, renal and middle cerebral artery blood flow velocity waveform indices) and to assess if the block modified fetal myocardial function.

PATIENTS AND METHODS

We studied eight healthy parturients in gestational weeks 38–42 with uncomplicated singleton pregnancies undergoing elective Caesarean section under extradural anaesthesia. The indications for Caesarean section were fetal breech presentation or feto–pelvic disproportion. The study was approved by the Ethics Committee of the University of Oulu. All patients were interviewed on the day before the operation; the aim of the study was explained, and informed consent was obtained.

When the patient had entered the operating theatre, the extradural space was identified at

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L2–3 or L3–4 with the patient in the left lateral position and a catheter was inserted 3 cm cephalad into the extradural space. Local anaesthetic was not injected. Patients then resumed a recumbent position with left uterine displacement and the first Doppler examination was started. Maternal uterine artery (main branch on the placental side of the uterus), the placental arcuate artery and fetal umbilical, middle cerebral and renal arteries were identified by a colour Doppler technique (Toshiba, model SSA-270A) and their blood velocity waveforms were recorded by the pulsed Doppler method (3.75-MHz sector probe). Three consecutive, correctly imaged blood velocity waveforms were analysed for the pulsatility index (PI) ((systolic peak velocity – end-diastolic velocity)/mean velocity during cardiac cycle). The fetal heart rate was measured from umbilical artery blood velocity waveforms.

The echocardiographic examination of the fetal heart was performed using a Toshiba SSA-270A scanner with a 3.75-MHz sector probe. M-Mode examination was made from a four-chamber view of the fetal heart by directing the M-mode cursor perpendicularly towards the interventricular septum at the level of the tips of the atrioventricular valves. The end-systolic (ES) and end-diastolic (ED) inner diameters of the ventricles were measured and the fractional shortenings of the ventricles ((ED – ES)/ED) were calculated. The systolic period was restricted to the time when the atrioventricular valves were closed on the M-mode screen. Mean circumferential shortenings of the ventricles, which allow the evaluation of the combined effect of fractional shortening with the duration of systole, were calculated also ((ED – ES)/ED × duration of systole). Three correctly imaged cycles were analysed and their mean values used for further analysis. The inner end-diastolic dimensions (IDD) of the ventricles represented the size of the fetal heart. Fractional and mean circumferential shortenings of the ventricles were calculated to assess the functional properties of the fetal heart. The fetal pulmonary trunk was identified by colour Doppler from the short axis view of the fetal heart through the base of the heart at the level of the origin of great vessels. The systolic peak velocity of the pulmonary trunk was measured by the pulsed Doppler system and the sample volume was placed just above the pulmonary valves. From the five-chamber view, the fetal ascending aorta was identified and systolic peak velocity of the aorta was measured just above the aortic valves. The angle between the transducer beam and the pulmonary trunk and aorta was less than 5°. Three consecutive, correctly imaged blood velocity waveforms were analysed and the mean values of the peak systolic velocities used for further analysis. One ultrasound measurement lasted an average of 26 min (range 19–32 min).

All patients were given supplementary oxygen by mask. Maternal ECG was monitored continuously and the arterial pressure and heart rate were measured at 5-min intervals at first. After induction of extradural block, maternal arterial pressure was measured every 2 min until delivery of the infant, using an automated arterial pressure device. Maternal hypotension was defined as a reduction in systolic arterial pressure greater than 30 mm Hg compared with the control value (the least value of systolic arterial pressure in the operating room before prehydration) or systolic arterial pressure less than 100 mm Hg. Hypotension was treated by increasing the infusion, and, if this was ineffective, by i.v. ephedrine.

Following a rapid infusion of 1 litre of balanced electrolyte solution, a test dose and further full dose of 0.5% bupivacaine were injected by fractional administration to obtain cephalad spread to T5. During the establishment of extradural block, a further 1 litre of balanced electrolyte solution was given i.v. The times required for the infusions of the electrolyte solution were noted.

Ultrasound measurement of maternal and fetal haemodynamic variables was repeated when sensory analgesia had reached the T5 level by following the same programme as at the first examination. All measurements were made by the same obstetrician (J.R.). Each patient served as her own control.

At delivery, Apgar scores were noted and samples of umbilical arterial and venous blood were collected for analysis of acid–base status.

For statistical analysis, Student's t test for paired data was used. Analysis was two-tailed, and $P < 0.05$ was accepted as statistically significant. Values are expressed as mean (SD).

RESULTS

Maternal arterial pressure remained unchanged during the study period. None of the patients received vasopressors. There was also no change in maternal heart rate (table I). The mean birth

TABLE I. *Maternal haemodynamic values. Lowest values (mean (SD)) before prehydration (1), during establishment of extradural anaesthesia (2), at the beginning of (3) and during (4) the second Doppler measurement*

	1	2	3	4
Systolic arterial pressure (mm Hg)	121 (11.6)	121 (13.0)	129 (12.1)	116 (14.6)
Diastolic arterial pressure (mm Hg)	70 (8.7)	73 (9.5)	73 (9.9)	71 (13.7)
Maternal heart rate (beat min^{-1})	79 (9.4)	82 (9.9)	79 (8.5)	76 (6.8)

TABLE II. *Mean (SD) fetal heart rate and blood velocity waveform indices (pulsatility index) of maternal uterine, placental arcuate, fetal umbilical, middle cerebral and renal arteries before and after extradural anaesthesia*

	Before extradural	After extradural	*P*
Fetal heart rate (beat min^{-1})	134 (0.08)	132 (0.10)	0.617
Pulsatility index			
Uterine artery	0.70 (0.09)	0.76 (0.15)	0.150
Arcuate artery	0.47 (0.16)	0.37 (0.05)	0.106
Umbilical artery	0.83 (0.21)	0.82 (0.21)	0.874
Middle cerebral artery	1.42 (0.33)	1.37 (0.18)	0.656
Renal artery	1.92 (0.36)	1.98 (0.45)	0.708

TABLE III. *Changes in fetal myocardial contractility and in ventricular sizes (mean (SD)) before and after extradural anaesthesia. IDD = inner end-diastolic dimension*

	Before extradural	After extradural	*P*
Left ventricle			
Fractional shortening (%)	32.5 (2.8)	35.4 (3.3)	0.123
Mean circumferential shortening (circ s^{-1})	1.31 (0.14)	1.42 (0.17)	0.268
IDD (mm)	17.0 (1.3)	16.2 (1.6)	0.139
Right ventricle			
Fractional shortening (%)	30.4 (2.6)	31.0 (2.8)	0.448
Mean circumferential shortening (circ s^{-1})	1.23 (0.18)	1.15 (0.14)	0.228
IDD (mm)	18.7 (2.4)	19.6 (2.7)	0.049
Pulmonary trunk			
Systolic peak velocity (cm s^{-1})	81.1 (13.5)	80.4 (11.3)	0.849
Ascending aorta			
Systolic peak velocity (cm s^{-1})	81.8 (12.9)	85.5 (11.1)	0.294

weight of the newborns was 3606 (599) g. The 1-min Apgar scores exceeded 8 in every infant. The smallest value of umbilical venous pH was 7.33, and all the umbilical arterial pH values were greater than 7.25 except for one (7.19).

The mean dose of bupivacaine was 22 ml (range 18–26 ml). The time required for infusion of the first 1 litre of electrolyte solution was 11 min (range 8–13 min) and that for the second 1 litre, 39 min (range 32–51 min). There were no significant changes in the PI of maternal uterine, placental arcuate or fetal umbilical artery after establishment of extradural anaesthesia. The PI of fetal renal or middle cerebral arteries did not change after extradural block. Fetal heart rate remained unchanged throughout the study (table II). Following extradural anaesthesia, both fractional and mean circumferential shortenings of the fetal cardiac ventricles remained unchanged. The left ventricular IDD did not alter significantly during the study, but the right ventricular IDD increased significantly ($P < 0.05$) after establishment of extradural anaesthesia. The systolic peak velocities of the pulmonary trunk and the ascending aorta did not change significantly during the study (table III).

DISCUSSION

The objective of this study was to examine uterine and fetal haemodynamic changes and fetal cardiac function in as versatile a manner as possible, by using modern ultrasonic Doppler methodology during extradural anaesthesia. The PI reflects reliably the peripheral vascular resistance in the arteries studied [7] and alteration in the index in the uterine and fetal arteries serves as a sensitive warning of fetal distress [8–10]. Changes in resistance in both maternal and fetal vessels may occur during obstetric anaesthesia as a result of maternal hypotension.

Our data suggest that uteroplacental and fetal haemodynamic states did not change after well-controlled extradural anaesthesia for elective Caesarean section in healthy parturients. This is in agreement with most earlier studies. Lindblad and co-workers [11] reported no change in the volume of fetal blood flow in the umbilical vein with the local anaesthetics studied. In the fetal descending aorta, blood flow increased when bupivacaine with adrenaline was used during extradural anaesthesia for Caesarean section, but no change occurred after etidocaine with adrenaline or plain bupivacaine. There were no significant changes in either uterine or umbilical blood flow velocity waveforms when lignocaine with adrenaline was used [4]. Extradural anaesthesia had no effect on the indices of the umbilical artery velocity waveform when chloroprocaine with adrenaline was used [2]. Long, Price and Spencer [3] found no significant changes in uteroplacental perfusion when plain bupivacaine was used for extradural anaesthesia. Giles, Lah and Trudinger [5] demonstrated a decrease in resistance in maternal uterine and fetal umbilical arteries, while in a more recent study Baumann and co-workers observed an increase in blood velocity waveform indices in the uteroplacental circulation, but not in the umbilical artery [6]. In both these studies, plain bupivacaine was used.

These conflicting results may be explained on the basis of different anaesthetic management and local anaesthetics. The adrenaline-containing solutions may modify maternal and fetal haemodynamics, even though no decrease was found in human intervillous blood flow after adrenaline 80–100 µg during extradural anaesthesia for Caesarean section [12]. The volume of preload infusion varied in these earlier studies from 1 to 2 litre and it is not clear how rapidly it was infused; furthermore the time interval between the two Doppler measurements was not measured. Lindblad and co-workers [11] gave ephedrine, which is known to induce marked changes in maternal cardiac output [13], to 17 of 27 patients. Baumann and others [6] used a smaller dose of 0.5% bupivacaine (14 ml) than that required usually for surgical extradural anaesthesia. Thus the extent of sympathetic block was less and probably its haemodynamic effects were less than in other studies. This could explain the increasing resistance of uterine arteries after extradural anaesthesia observed in their study.

In the present study, the preload infusion of 2 litre of electrolyte solution was accomplished as rapidly as possible to obtain a maximal intravascular volume expanding effect. There was no delay in locating the extradural space between measurements because the extradural catheter was inserted before the examinations. No significant changes were observed in any variables measured except for the increase in the IDD of the right ventricle of fetal heart and it is not clear if this reflected the volume status of the fetus after maternal hypervolaemia. The stability of uterine and fetal haemodynamics was also consistent with normal Apgar scores and acid–base values in umbilical blood after delivery.

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OPTIMAL DOSE OF LIGNOCAINE FOR PREVENTING PAIN ON INJECTION OF PROPOFOL

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SUMMARY

The purpose of this study was to define the optimum dose of lignocaine required to reduce pain on injection of propofol. We conducted a prospective, randomized, double-blind trial on 310 patients undergoing anaesthesia. Patients were allocated to four groups according to the lignocaine dosage: group A (control), no lignocaine; group B, lignocaine 0.1 mg kg^{-1}; group C, lignocaine 0.2 mg kg^{-1}; group D, lignocaine 0.4 mg kg^{-1}. Our results showed that a dose of lignocaine 0.1 mg kg^{-1} significantly reduced the incidence of pain and that there was no improvement when the dose was increased.

KEY WORDS

Anaesthetics, intravenous. propofol. Complications: pain.

Propofol is a rapidly acting i.v. agent used for induction of anaesthesia. It has many advantages and a low incidence of side effects [1]; but pain induced by injection of propofol limits its use [2, 3]. The pain was attributed first to the solubilizing agent, Cremophor EL, which is implicated in anaphylactoid reactions, but it persisted when this was replaced by soya bean oil [4, 5]. Several authors have shown that i.v. lignocaine given before or with propofol reduced the frequency of pain [4, 6, 7], but did not suppress it completely. The dose of lignocaine used varied and was based on the doses used in prevention of pain induced by other anaesthetic drugs such as etomidate [8]. The purpose of this study was to evaluate the optimal dose of lignocaine for reducing pain associated with i.v. administration of propofol.

PATIENTS AND METHODS

The study comprised a prospective, randomized, double-blind trial, approved by the Hospital Ethics Committee. All patients gave their informed written consent and none had a history of adverse response to propofol or lignocaine. We studied 310 patients (150 male) aged 18–80 yr (mean 53.1 yr), ASA class I or II, undergoing a general anaesthesia for diagnostic procedures or minor surgery. Except for premedication, patients received no analgesic or sedative drug in the 12 h before the study. One hour before anaesthesia, patients were premedicated with hydroxyzine 100 mg i.m. and cimetidine 400 mg orally (PM1), or with midazolam 5 mg and atropine 0.5 mg i.m. (PM2). In the operating room, an 18-gauge i.v. cannula was inserted into a large forearm vein and standard monitoring commenced. Anaesthesia was induced with propofol 2.5 mg kg^{-1}, mixed in the syringe (20 ml) with sodium chloride (group A), or lignocaine 0.1 mg kg^{-1} (group B), 0.2 mg kg^{-1} (group C) or 0.4 mg kg^{-1} (group D). In all groups the syringe was filled to 20 ml with sodium chloride. The solution was injected slowly (30 s) within 30 min of preparation of the mixture. Three different members of the anaesthesia team took responsibility for anaesthesia, preparation of the mixture, and recording of pain on injection. Anaesthesia was maintained with a continuous perfusion of propofol without lignocaine and with 50% nitrous oxide in oxygen.

Arterial pressure, heart rate and Sp_{O_2} were

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recorded every 5 min (HP52801) and the ECG was monitored continuously. At initial injection, the degree of pain experienced by the patient was scored as follows: 0 = no pain complained of even when asked about after injection; 1 = patient complained of pain when asked after injection of 50 % of the total dose; 2 = spontaneous complaint by patient before injection of 50 % of total dose; 3 = reported pain was associated with grimacing, withdrawal movement of the forearm, or both.

Data were analysed by chi-square test (sex ratio, ASA, PM1/PM2, degree of pain), Student's *t* test (age, weight, duration of anaesthesia, arterial pressure, heart rate) and a non-parametric test (Mann–Whitney test) when the groups studied were too small. $P < 0.05$ was considered significant.

RESULTS

There were no significant differences between the four groups in age, weight, sex, ASA physical status, premedication and duration of anaesthesia (table I). Haemodynamic changes were similar in the four groups (table II) and no patient developed cardiac events associated with lignocaine. Injection of propofol alone (group A) induced pain scores of 1, 2 and 3 in 20.7 %, 10.3 % and 5.1 % of patients, respectively. In group B (lignocaine 0.1 mg kg^{-1}), the incidence of pain was reduced significantly. There was no significant difference between group B and groups C (lignocaine 0.2 mg kg^{-1}) and D (lignocaine 0.4 mg kg^{-1}) (table III).

TABLE I. *Patient characteristics (number or mean (SD)). PM1 = Premedication with hydroxyzine 100 mg i.m. plus cimetidine 400 mg orally; PM2 = premedication with midazolam 5 mg and atropine 0.5 mg i.m. No significant difference between the four groups*

	Group A ($n = 77$)	Group B ($n = 86$)	Group C ($n = 71$)	Group D ($n = 76$)
Age (yr)	50.5 (9.4)	51.2 (8.6)	50.9 (10.5)	52.0 (9.6)
Weight (kg)	60.6 (9.7)	58.2 (9.5)	62.2 (9.9)	59.1 (8.1)
Sex (M/F)	40/37	44/42	37/34	36/30
ASA I/II	62/15	75/11	57/14	64/12
PM1/PM2	60/17	74/12	56/15	62/14
Duration of anaesthesia (min)	20.9 (6.9)	18.9 (7.5)	19.1 (8.2)	21.1 (5.3)

TABLE II. *Mean (SD), mean arterial pressure (MAP) and heart rate (HR) just before and 5 and 10 min after induction of anaesthesia. No significant difference between the four groups*

	Group A ($n = 77$)	Group B ($n = 86$)	Group C ($n = 71$)	Group D ($n = 76$)
Before induction				
MAP (mm Hg)	92 (14)	91 (13)	95 (10)	91 (15)
HR (beat min^{-1})	82 (15)	78 (13)	81 (14)	80 (11)
5 min after induction				
MAP (mm Hg)	70 (15)	69 (11)	71 (10)	68 (9)
HR (beat min^{-1})	66 (12)	66 (10)	64 (11)	67 (8)
10 min after induction				
MAP (mm Hg)	82 (12)	84 (13)	80 (16)	85 (11)
HR (beat min^{-1})	62 (11)	68 (11)	65 (12)	63 (10)

TABLE III. *Patients feeling pain on i.v. injection of propofol in the control and lignocaine groups. For each score of pain, a significant difference ($P < 0.05$) was found between group A (control group) and the other groups, but no significant difference was found between group B (lignocaine 0.1 mg kg^{-1}), group C (lignocaine 0.2 mg kg^{-1}) and group D (lignocaine 0.4 mg kg^{-1})*

Pain score	Group A ($n = 77$)		Group B ($n = 86$)		Group C ($n = 71$)		Group D ($n = 76$)		Total ($n = 310$)	
	No.	%	No.	%	No.	%	No.	%	No.	%
0	49	63.6	73	84.8	58	81.6	62	81.5	242	78
1	16	20.7	7	8.1	7	9.8	8	10.5	38	12.2
2	8	10.3	5	5.8	6	8.4	6	7.8	25	8
3	4	5.1	1	1.1	0	0	0	0	5	1.6

DISCUSSION

We have shown that a dose of lignocaine 0.1 mg kg^{-1} injected with propofol was associated with a significantly smaller incidence of pain than that in the control group and that an increase in dose did not provide better results. Pain on injection of propofol is a well recognized problem, with a high frequency (30–80 %) [7, 9]. Our patients in group A confirmed these data (36.3 %). Reformulation in soya bean oil to replace the solvent Cremophor EL (which has been implicated in the incidence of pain) was shown to have little effect with propofol [2, 10], although this almost completely prevented pain with diazepam [11] and etomidate [12].

Factors such as the vein used and the rate of injection have been studied previously: injection into a vein on the dorsum of the hand is more painful than injection into a large vein in the antecubital fossa [3, 10, 13]. If injected slowly, however, propofol causes more pain, which usually does not occur immediately after injection [10]. Thus pain on injection of propofol results not only from a direct effect on the vein wall, but involves mediators such as kininogens [10, 14]. This is confirmed by the infrequent occurrence of thrombophlebitis and the wide variation between animal species in the pain response to injection of propofol [10].

Several attempts have been made to reduce the incidence of pain, such as prior administration of opioids [15] or aspirin [16], the use of a large-gauge cannula [10], injection into a large vein rather than one on the dorsum of the hand [5], 50% dilution in a glucose solution [14], and the use of EMLA cream applied to the skin 1 h before cannulation [6]. The data from all these studies are difficult to compare because of variation in study design. In our study, propofol was administered to all patients in the same manner, with standardization of rate of injection, site of injection in the antecubital fossa and size of cannula. Injection into the dorsum of the hand would have given more striking results but could have changed the rate of administration in some cases.

The use of lignocaine was found to reduce the incidence of pain to 5% when propofol was injected into a vein on the dorsum of the hand [4, 6, 7], provided that lignocaine was injected in combination with, and not before, the propofol —suggesting that an indirect mechanism is involved [4, 5]. Although the incidence of pain in our study was greater (15–18%), our method differed from that of other studies: no patient received opioids, and injection was slower and performed in a large vein of the forearm.

We conclude that the incidence of pain on injection of propofol may be reduced by addition of lignocaine. The optimum dose of lignocaine was found to be 0.1 mg kg^{-1} and its action may involve stabilization of pain mediators such as kininogens.

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RESPIRATORY COMPLICATIONS AND HYPOXIC EPISODES DURING INHALATION INDUCTION WITH ISOFLURANE IN CHILDREN

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SUMMARY

We have studied the incidence of respiratory complications and hypoxic episodes during inhalation induction with isoflurane in 75 healthy unpremedicated children. Problems occurred less frequently when 4% isoflurane in oxygen was used from the outset than with traditional techniques using nitrous oxide and a gradually increasing inspired vapour concentration. The improved results observed with the former method may be secondary to more rapid uptake of vapour so that the second stage of anaesthesia characteristic of anaesthetic ethers is shortened considerably.

KEY WORDS

Anaesthesia: paediatric. Anaesthetic techniques: inhalation induction. Anaesthetics, volatile: isoflurane. Complications: respiratory.

Inhalation induction with isoflurane in unpremedicated children using a technique incorporating nitrous oxide, oxygen and a gradually increasing inspired vapour concentration is accompanied frequently by respiratory complications and hypoxic episodes [1, 2]. We wished to determine if modifications to this "traditional" induction technique affected the incidence of these adverse occurrences.

PATIENTS AND METHODS

Institutional Ethics Committee approval was given for the study and informed parental consent obtained in each case. The study population consisted of 75 healthy children undergoing elective surgery on a day-case basis under general anaesthesia.

No premedication was administered. After arrival in the operating theatre area, each child was allocated randomly (using a table of random numbers) to induction of anaesthesia by one of the three techniques described below. Each patient's age, weight and sex were noted. Pre-induction arterial oxygen saturation (Sp_{O_2}) was recorded by pulse oximeter for 1 min after steady readings were obtained. In each case, induction was performed by the same anaesthetist who was blind to the oximeter display, but was informed if Sp_{O_2} was $< 91\%$. All recordings were made by an independent observer.

In group A children ($n = 23$) anaesthesia was induced with isoflurane and 60% nitrous oxide in oxygen. The initial inspired isoflurane concentration was 0.5% and was increased by 0.5% every 10 breaths to a maximum of 4%, at which concentration induction was continued until complete. In children in group B ($n = 23$), anaesthesia was induced in an identical manner until an isoflurane concentration of 2% was reached. This concentration was maintained for 2 min, following which induction proceeded as in group A. In group C children ($n = 29$), anaesthesia was induced from the outset with 4% isoflurane in oxygen. In this group, no alterations were made to the composition of the inspired gas mixture before completion of induction.

An Ayre's T-piece with Jackson-Rees' modification was used for induction in all groups, with a fresh gas flow sufficient to prevent rebreathing. The anaesthetic mixture was administered at first with the aid of a cupped hand over the child's

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mouth and nose; when the eyelash reflex could not be elicited an anaesthetic face-mask of appropriate size was applied gently. Induction was judged to be complete when the child was unconscious and breathing regularly, with eyes fixed and central, and pupils constricted.

Sp_{O_2} and inspired vapour concentration were recorded every 15 s during induction. Any events of coughing, breath-holding or laryngospasm were noted, together with the lowest Sp_{O_2} associated with these events. Time taken to induce anaesthesia was recorded.

Age and weight were tested for statistical significance by analysis of variance; if a difference in the means was found, further analysis was carried out with Student's unpaired *t* test. The Kruskal–Wallis and Mann–Whitney *U* tests were used for non-parametric data (Sp_{O_2}, induction time, relationship between occurrence of respiratory complications and trough Sp_{O_2} during induction). Nominal data (sex distribution, incidence of respiratory complications) were tested using the chi-square test with Yates' correction. $P < 0.05$ was taken as significant.

RESULTS

The three groups were similar in age, sex distribution and pre-induction Sp_{O_2}. Group A children weighed less than those in groups B and C ($P < 0.05$) (table I).

TABLE I. *Patient characteristics: age, weight, pre-induction* Sp_{O_2} *(mean (SEM or range)) and sex distribution.* *$P < 0.05$ *for group A compared with groups B and C*

Group	Age (yr)	Weight (kg)	Pre-induction Sp_{O_2} (%)	Sex (M/F)
A ($n = 23$)	2.9 (1.0–5.0)	12.8 (0.6)*	98 (1.7)	14/9
B ($n = 23$)	3.2 (1.2–6.0)	15.0 (0.6)	98 (1.3)	19/4
C ($n = 29$)	2.9 (1.0–5.1)	14.6 (0.6)	98 (1.3)	21/8

TABLE III. *Incidence of respiratory complications.* *$P < 0.05$ *for group C compared with groups A and B;* **$P < 0.01$ *for group C compared with groups A and B. No significant difference between group A and group B*

Group	Overall	Coughing	Breath-holding	Laryngospasm
A	12	10	2	2
B	13	9	5	4
C	5**	4*	1	—

Induction time was shorter for group C children than for those in the other two groups. Eight of 23 children in group A and seven of 23 in group B had desaturation to less than 91% during induction, compared with one of 29 in group C (table II). The difference between group C and groups A and B was significant for both induction time and trough Sp_{O_2} ($P < 0.0005$).

Group C children had a lower overall incidence of respiratory complications during induction than others ($P < 0.01$) (table III). The incidence of coughing was lower in group C ($P < 0.05$), but no significant difference between groups was present for either breath-holding or laryngospasm. The overall incidence of respiratory problems for children in groups A and B was less than the sum total of each individual occurrence (some patients developed more than one of the three complications for which observations were made). The difference between groups A and B was not significant for any of the adverse occurrences described.

Trough Sp_{O_2} during induction was lower in the 30 children who developed respiratory complications than in the 45 children who did not ($P < 0.0001$). Further analysis revealed that this was true for patients in groups A and B only. Group C children tended not to exhibit desaturation even in the presence of respiratory complications (table IV).

TABLE II. *Induction time (median (range)) and distribution of trough* Sp_{O_2} *during induction. Difference between group C and groups A and B significant for both induction time and trough* Sp_{O_2} ($P < 0.0005$ *for each). Differences between group A and group B not significant*

Group	Induction time (min)	Trough Sp_{O_2} during induction (%)			
		(91–100)	(81–90)	(71–80)	(< 71)
A	8.25 (5.75–16.75)	15	3	3	2
B	9.75 (6.75–15.25)	16	3	2	2
C	6.75 (4.0–10.0)	28	—	1	—

TABLE IV. *Trough Sp_{O_2} during induction in children with and without respiratory complications. Expressed as number of patients (median trough Sp_{O_2}%). Difference for "all children" significant ($P < 0.0001$). Difference for both group A and group B significant ($P < 0.05$ for each). No significant difference in group C*

	All children	Group A	Group B	Group C
Complications	30 (91)	12 (87)	13 (90)	5 (96)
No complications	45 (96)	11 (95)	10 (96)	24 (97)

DISCUSSION

Inhalation induction of anaesthesia is popular for young children. Sedative premedication reduces the incidence of adverse occurrences when isoflurane is used for this purpose [3]. However, much paediatric surgery is carried out on an outpatient basis, so that the use of long-acting premedicant drugs may not always be appropriate. The induction method we used in group A children is similar to that described by previous workers [1, 2]. That used in group B was chosen because some believe that the incidence of airway problems during isoflurane induction is reduced if the inspired concentration is increased more slowly [4]. This latter technique conferred no obvious benefit over the group A method. Induction with isoflurane in oxygen has been used previously in children [5–7] but has not been compared directly with other techniques before the present study.

The advantages of the method used in group C patients may be summarized as follows: better oxygenation during induction, even if respiratory complications occur; shorter induction time; and lesser incidence of respiratory complications during induction. The first of these is related probably to both the inspired oxygen concentration used and the reduction in incidence of respiratory problems (table IV). Only one child in the entire study (in group A) had a trough Sp_{O_2} value less than 91% without a co-existing respiratory complication. Previous workers have found that, despite its lesser blood-gas solubility coefficient, isoflurane produces inhalation induction more slowly than halothane [2, 8]. This has been attributed to the greater incidence of respiratory problems with this agent [8]—a view that appears to have been borne out by the present study, in which the onset of these problems invariably prolonged induction. It seems, therefore, that the shorter induction times in group C children may be attributed also to the reduced incidence of respiratory complications in this group.

It is not entirely clear why children in group C were less likely to develop respiratory problems. There is little reason to suppose that use of a high inspired oxygen concentration was responsible, although this technique would undoubtedly lead to increased oxygen reserves during induction, thus tending to maintain Sp_{O_2} for some time in the presence of complications. This probably explains why the incidence of desaturation was low in group C children who developed signs of airway irritation.

Could nitrous oxide have been responsible for the greater incidence of respiratory complications in groups A and B? This agent has been used by anaesthetists for almost 150 years and there is little, if any, evidence to indicate that it is an airway irritant and likely to provoke coughing, breath-holding or laryngospasm. Moreover, it has been demonstrated that uptake of volatile anaesthetic agents is accelerated by concurrent administration of nitrous oxide [9]. It may be that use of 4% isoflurane in an oxygen–nitrous oxide mixture would provide a more rapid induction than that in our group C children, without any increase in the incidence of respiratory complications and hypoxic episodes. This has been shown to be the case where nitrous oxide was added to a 5% halothane in oxygen mixture for single breath induction of anaesthesia in older children [10].

If the improved results seen in group C were related to neither inspired oxygen concentration nor omission of nitrous oxide, the use of 4% isoflurane must have been responsible as, apart from the slightly lesser weight of group A children, this was the only other variable compared with the other two groups. On preliminary consideration, this might appear unlikely, as the pungent ethereal odour of isoflurane is well recognized and is thought to be responsible for both the high incidence of airway irritation and the prolonged induction time observed previously with this agent in comparison with halothane [2]. One might expect, therefore, a greater incidence of respiratory complications and a greater prolongation of induction time when a high inspired isoflurane concentration is used from the outset. However, pungency may not be the relevant factor—it has been suggested that airway reactions during inhalation induction are more a reflection of the second stage of anaesthesia than a reaction to the pungency of the agent used [11]. Episodes of movement and excitement, representing the classical stage two of an ether anaesthetic, are common during inhalation induction with isoflurane [12] and may bear some relationship to the incidence of respiratory complications. If this unpleasant second stage could be shortened because of more rapid uptake of anaesthetic agent, the end result might be a reduction in the incidence of respiratory problems during induction. This would appear to have been achieved in an adult study comparing single vital capacity breath (VCB) induction of anaesthesia using 2% isoflurane in oxygen and nitrous oxide with a technique utilizing an initial mixture of 0.5% isoflurane in oxygen and nitrous oxide, the inspired isoflurane concentration being increased gradually as induction proceeded [13]. Coughing, breath-holding, laryngospasm and movement during induction were all less common in the single VCB group. Unfortunately, single VCB induction is not a realistic option for children younger than 6 yr, because of the degree of patient understanding and co-operation required. However, the use of a high inspired concentration of isoflurane from the outset, as in group C children in the present study, represents a compromise and achieves also a rapid induction of anaesthesia without increased incidence of complications.

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IS THE END-TIDAL PARTIAL PRESSURE OF ISOFLURANE A GOOD PREDICTOR OF ITS ARTERIAL PARTIAL PRESSURE?

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SUMMARY

End-tidal partial pressure of isoflurane (PE'_{iso}) *may be used as a measure of anaesthetic depth. During uptake, an arterial partial pressure* (Pa_{iso}) *which is considerably less than* PE'_{iso} ($Pa_{iso}/PE'_{iso} \leqslant 1$) *leads to underestimation of depth of anaesthesia and, during elimination,* $PE'_{iso}/Pa_{iso} \leqslant 1$ *will lead to an overestimation of anaesthetic depth. We measured* Pa_{iso}/PE'_{iso} *during a 60-min uptake period of 1% isoflurane and* PE'_{iso}/Pa_{iso} *during the subsequent 60-min elimination period in 26 patients (age 13–88 yr, ASA I–III) undergoing various surgical procedures. After 15 min of isoflurane uptake,* Pa_{iso}/PE'_{iso} *of 26 patients was mean 0.78 (SD 0.10) and this increased only marginally at 60 min (0.79 (0.09)), whereas during elimination,* PE'_{iso}/Pa_{iso} *was in the range 0.79 (0.14)–0.83 (0.11). Predictability of* Pa_{iso} *in a given patient is hindered by the high SD of* Pa_{iso}/PE'_{iso} *and* PE'_{iso}/Pa_{iso}*, but it may be improved by taking into account age, ASA physical status category, vital capacity, inspired minus end-tidal isoflurane partial pressure and arterial minus end-tidal carbon dioxide partial pressure during uptake; and obesity, end-tidal isoflurane partial pressure and arterial minus end-tidal carbon dioxide partial pressure during elimination. However, even with multiple regression analysis (to account for the various possible variables), clinically useful prediction of* Pa_{iso}/PE'_{iso} and PE'_{iso}/Pa_{iso} *in a particular patient is not possible (residual SD 0.084 and 0.113, respectively).*

KEY WORDS

Anaesthetics, volatile: isoflurane. Pharmacokinetics uptake, recovery

The pharmacokinetics of isoflurane have been studied in animals [1] and healthy human volunteers [2]. In the latter, no significant alveolar–arterial partial pressure difference was evident. This may be explained by the fact that the usual changes in pulmonary gas exchange observed after induction of anaesthesia [3,4] did not occur in the volunteers, as they inhaled only subanaesthetic concentrations of isoflurane. In another study, in which volunteers inhaled anaesthetic concentrations of halothane, a significant alveolar–arterial partial pressure difference was found [5] and, consequently, a similar difference should be expected for isoflurane. Such data have been published in a study of healthy patients under isoflurane anaesthesia [6]. However, in a heterogeneous patient population this difference might be larger and related to specific patient characteristics.

The present study was performed to investigate differences between arterial and end-tidal partial pressures of isoflurane during uptake and elimination of isoflurane in a mixed patient population undergoing surgery. The relationship between this difference and age, ASA physical status category, obesity, vital capacity (VC), forced expiratory volume in the first 1 s (FEV_1), history of smoking habits, physical examination, chest x-ray and position of the patient on the operating table was also investigated. In addition, isoflurane partial pressure differences were compared with those of carbon dioxide.

PATIENTS AND METHODS

We studied 26 patients (16 female, 10 male; aged 13–88 yr (mean 53 yr)) undergoing elective plastic, orthopaedic, abdominal, or urological surgery

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of at least 3 h duration, requiring invasive arterial pressure monitoring. All patients gave written informed consent and the study was approved by the local Ethics Committee.

Patients undergoing neuro- and cardiopulmonary surgery, and those with known coronary heart disease were excluded.

The patient's gender and any history of productive cough, wheezing and smoking habits were noted. Physical examination and a chest x-ray were performed. Lung function was tested by measuring vital capacity (VC) and forced expired volume in the first 1 s (FEV_1) using a computer pneumotachograph (Pneumoscreen, Jaeger, elektromagnetische Gerätefabrik, Würzburg, Germany). Position on the operating table was noted (supine or lateral).

In patients younger than 60 yr, premedication consisted of morphine 0.1 mg kg^{-1} and hyoscine 0.005 mg kg^{-1}. Premedication was not given to patients older than 60 yr. Anaesthesia was induced with propofol 2 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} and alfentanil 0.5 mg, followed by tracheal intubation and ventilation of the lungs with 100 % oxygen. Anaesthesia was maintained by a continuous infusion of propofol 6 mg kg^{-1} h^{-1}. Clinical signs of light anaesthesia were treated with alfentanil in bolus doses of 0.5–1.0 mg. Ventilation of the lungs was performed using a Siemens 900C ventilator at a rate of 6 b.p.m. and a tidal volume of 8–12 ml kg^{-1} body weight to maintain end-tidal $P\text{CO}_2$ at 4.2–4.8 kPa. Arterial pressure was monitored via a 20-gauge catheter in the radial artery and recorded every 5 min. ECG, nasopharyngeal temperature, degree of muscle relaxation (train-of-four) and inhaled oxygen concentration were monitored. After a minimum of 30 min following the initial bolus of propofol, surgery was started.

Five to 10 minutes later, isoflurane was introduced into the system at a constant inspired concentration of 1.0 %. It was discontinued after 60 min and elimination was studied during the following 60 min. Arterial blood samples were taken for measurement of carbon dioxide and isoflurane partial pressures 5 min before and 1, 3, 5, 10, 15, 20, 30, 45 and 60 min after the start of isoflurane administration, and 1, 3, 5, 10, 15, 20, 30, 45 and 60 min after discontinuing isoflurane.

End-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$), inspired and end-tidal isoflurane partial pressures ($P\text{I}_{iso}$, $P\text{E}'_{iso}$) were measured with Beckman LB2 analysers by aspirating gas (flow rate of 500 ml min^{-1} each) from the connection between the tracheal tube and the Y-piece of the breathing system. The instruments were calibrated before each experiment. End-tidal partial pressures were determined using peak detection. Data were recorded continuously on a three-channel recorder (YEV3056 pen recorder, Yokogawa Hokushin Electric, Japan).

The blood samples were placed on ice, and Pa_{CO_2} was analysed within 45 min after blood collection with an IL System 1302 blood-gas analyser; the values were corrected for the patient's temperature [7].

A slight modification of the method described by Zbinden and colleagues [8] was used for measuring the partial pressure of isoflurane in arterial blood (Pa_{iso}). As it was not always possible to withdraw the exact quantity of 0.5 ml of blood during rapid blood sampling, the weight of the vials was determined before and after sampling to ensure that the exact amount of blood withdrawn was known, so that all gas chromatographic measurements could be corrected to 0.5 ml of blood. All measurements of isoflurane partial pressure were made at 37 °C ($P37_{iso}$). Because temperatures of some of the patients decreased considerably, temperature correction of the values was necessary. A separate study to determine the temperature correction factor was performed.

Blood from five volunteers was tonometered with 1 % isoflurane. Equilibration for at least 15 min was allowed at temperatures of 33, 35, 37 and 39 °C. Two blood samples of 0.5 ml each were withdrawn from the tonometer at each temperature, placed into a 5-ml vial and equilibrated with the headspace at the corresponding temperature. Headspace samples were measured in duplicate by gas chromatography. The coefficient of variation was 2.8 %. The temperature correction for isoflurane partial pressure was shown to follow an exponential course:

$$Pa_{iso} = P37_{iso} \cdot 10^{0\ 0135\,(t-37)}$$

where Pa_{iso} is the partial pressure at the patient's temperature, t °C. This temperature coefficient (−3.16 per cent/°C between 37 and 36 °C) agrees with that predicted for isoflurane in water from values for other agents (−3.10 per cent/°C) [9] or with directly measured values (−4.36 per cent/°C) [10].

Definitions and data analysis

Abnormal weight was defined as more than

120% of the ideal weight for each patient [11]. The lower limits of normal VC and FEV_1 were defined as a point located 1.64 RSD (= residual standard deviation = standard error of the estimate) below the mean value for subjects of the same height, sex and age on the regression line [12–14]. The history was defined as either normal or abnormal (= recent history of productive cough, wheezing or smoking of more than 5 cigarettes per day). Physical examination was defined as either normal or abnormal (= wheezing or rales). Chest x-ray was defined as either normal or abnormal (= definitive lung pathology such as emphysema, atelectasis, etc.).

The ratio and the difference between $P\text{E}'_{\text{CO}_2}$ and Pa_{CO_2} were calculated ($P\text{E}'_{\text{CO}_2}/Pa_{\text{CO}_2}$ and $Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$, respectively). During isoflurane uptake, the following calculations of isoflurane partial pressure were performed: end-tidal to inspired ($P\text{E}'_{\text{ISO}}/P\text{I}_{\text{ISO}}$), arterial to inspired ($Pa_{\text{ISO}}/P\text{I}_{\text{ISO}}$), inspired minus end-tidal ($P\text{I}_{\text{ISO}} - P\text{E}'_{\text{ISO}}$), arterial to end-tidal ($Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}}$) and end-tidal minus arterial ($P\text{E}'_{\text{ISO}} - Pa_{\text{ISO}}$). End-tidal to arterial and arterial minus end-tidal partial pressures of isoflurane ($P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}}$ and $Pa_{\text{ISO}} - P\text{E}'_{\text{ISO}}$, respectively) were calculated during elimination. $Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}}$, $P\text{E}'_{\text{ISO}} - Pa_{\text{ISO}}$, $P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}}$ and $Pa_{\text{ISO}} - P\text{E}'_{\text{ISO}}$ are referred to as "estimates of Pa_{ISO}" in the text.

In order to analyse the effect of patient characteristics on isoflurane partial pressure, it was necessary to have only one value for the uptake or elimination period for each patient. Because the ratio $Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}}$ was constant between 20 and 60 min of uptake and between 61 and 120 min of elimination (fig. 2), the mean value for each patient was calculated during the two periods ($(Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}})_{20-60}$ and $(P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}})_{61-120}$, respectively). The influence of age (continuous scale data) on these two variables was studied by linear regression. All the other patient characteristics are expressed on an ordinal scale, therefore analysis of variance was used to study the effect on $(Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}})_{20-60}$ and $(P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}})_{61-120}$.

Linear regression analysis was used first to study the relation between the estimates of Pa_{ISO} and each of the various independent variables ($P\text{I}_{\text{ISO}} - P\text{E}'_{\text{ISO}}$ during uptake, $P\text{E}'_{\text{ISO}}$ during elimination and $Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$ and $P\text{E}'_{\text{CO}_2}/Pa_{\text{CO}_2}$ during both time periods). Multiple regression analysis was then tried to improve prediction of each estimate of Pa_{ISO} during uptake and elimination. All independent variables which could contribute to a better prediction were included and a stepwise elimination of the most insignificant variables was performed. Patient characteristics were computed as either a continuous variable (age) or "dummy variables" (with two dummy variables for ASA classification, because there are three levels of the nominal scale, and one dummy variable for all the other patient characteristics (normal *vs* abnormal and supine *vs* lateral)) [15]. There are 18 measurements for each patient but only one value for a specific patient characteristic. We solved this problem by attributing the specific patient characteristic to each of the nine measurements during the respective time period.

RESULTS

During isoflurane uptake a rapid increase in $Pa_{\text{ISO}}/P\text{I}_{\text{ISO}}$ and $P\text{E}'_{\text{ISO}}/P\text{I}_{\text{ISO}}$ was observed (fig. 1); after 10 min, more than 80% of the values present at 60 min were reached. However, even after 60 min of isoflurane uptake, a significant difference between $P\text{E}'_{\text{ISO}}$ and $P\text{I}_{\text{ISO}}$, and between $P\text{E}'_{\text{ISO}}$ and Pa_{ISO} persisted.

During elimination, both $P\text{E}'_{\text{ISO}}$ and Pa_{ISO} decreased rapidly and reached 20% of $P\text{I}_{\text{ISO}}$ at the end of the uptake period after approximately 10 min. As expected, $P\text{E}'_{\text{ISO}}$ was always smaller than Pa_{ISO} and there was a persistent difference between $P\text{E}'_{\text{ISO}}$ and $P\text{I}_{\text{ISO}}$ and between Pa_{ISO} and $P\text{E}'_{\text{ISO}}$ after 60 min. Figure 2 shows the mean ratios $Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}}$ (during uptake) and $P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}}$ (during elimination).

After 20 min of isoflurane uptake, $Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}}$ reached the value of 0.78 and remained constant during the rest of the uptake period. Throughout elimination, the mean value of all $P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}}$ was 0.80, with only small deviations from this value at each particular sampling time. However, the SD of these ratios increased as time progressed, possibly because of an increased error in isoflurane measurement at very small partial pressures and, therefore, a larger fluctuation of the $P\text{E}'_{\text{ISO}}/Pa_{\text{ISO}}$ ratio.

The heterogeneity of the patient population in terms of age, ASA physical status category, weight, etc., is depicted in table I.

During the uptake period there was a significant correlation between the age of the patient and $(Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}})_{20-60}$ (table II). The ASA physical status category was related also to small values of $(Pa_{\text{ISO}}/P\text{E}'_{\text{ISO}})_{20-60}$, with a significant difference between the first and second and the first

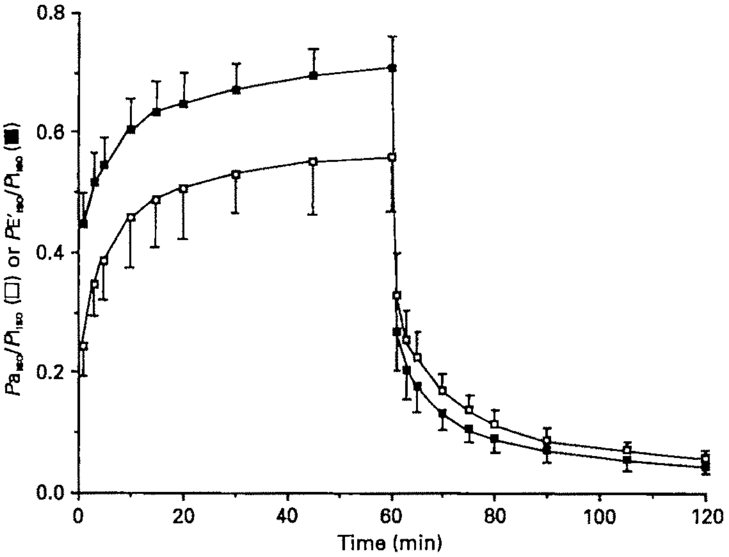

FIG. 1. Uptake and elimination of isoflurane shown as mean (SD) values of the ratios arterial to inspired (Pa_{iso}/PI_{iso}) and end-tidal to inspired (PE'_{iso}/PI_{iso}) isoflurane partial pressures of isoflurane of 26 patients.

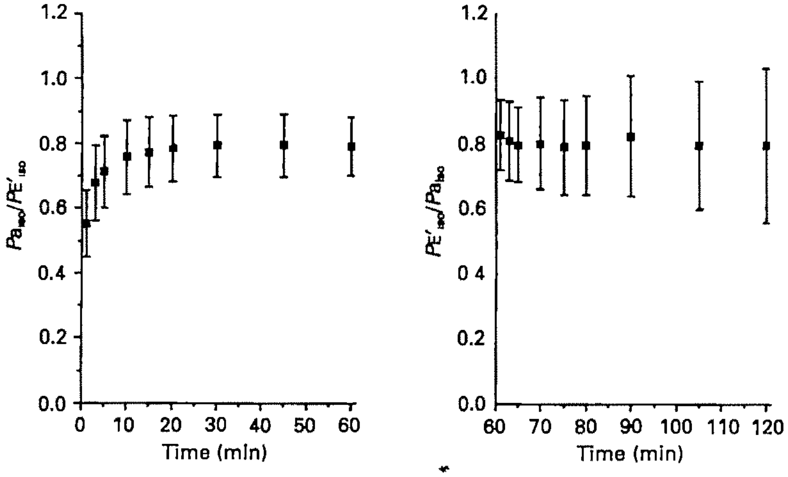

FIG. 2. The means (SD) of the ratios Pa_{iso}/PE'_{iso} (during uptake, left) and PE'_{iso}/Pa_{iso} (during elimination, right) plotted against time. Except during the first 10 min of the uptake period, the values remain relatively constant, although the SD values indicate considerable interindividual variation.

TABLE I. *Patient characteristics. F = female; M = male; N = normal; A = abnormal; S = supine; L = lateral*

Patient No.	Sex	Age (yr)	ASA	% Ideal weight	VC	FEV_1	History	Physical examination	x-Ray	Position	Surgery
1	F	23	II	93	N	N	A	N	N	S	Mammoplasty
2	F	51	I	105	N	N	N	N	N	S	Mammoplasty
3	F	60	II	108	N	N	N	N	N	S	Pancreatic cyst
4	F	33	II	115	N	N	N	N	N	S	Cholecystectomy
5	M	72	II	90	A	N	N	N	N	S	Hip prosthesis
6	F	21	II	112	A	A	N	N	N	L	Internal fixation of pelvis
7	F	83	II	137	A	N	A	N	N	L	Nephrectomy
8	M	67	II	108	A	A	A	N	N	S	Urethral sphincteroplasty
9	M	13	I	74	A	N	N	N	N	L	Abdominal lymphadenectomy
10	M	50	III	127	A	A	A	A	A	L	Nephrectomy
11	F	69	II	97	A	N	N	N	N	S	Internal fixation of tibia
12	M	46	I	134	N	N	A	A	A	S	Hip prosthesis
13	F	31	I	113	N	A	N	N	N	S	Mammoplasty
14	M	56	II	141	A	A	N	N	N	S	Hip prosthesis
15	F	53	II	126	N	N	A	A	A	L	Fundoplication
16	M	63	II	156	A	A	A	A	A	S	Hemicolectomy
17	F	79	II	95	A	N	N	N	N	S	Cholecystectomy
18	F	88	III	114	N	N	N	A	A	S	Hip prosthesis
19	M	32	I	112	N	N	N	N	N	S	Internal fixation of calcaneus
20	F	46	II	106	N	A	N	N	N	S	Anterior resection (rectum)
21	F	80	II	96	A	N	N	N	N	S	Hemicolectomy
22	F	36	II	148	N	N	N	N	N	S	Fundoplication
23	F	26	I	93	N	N	A	N	N	S	Mammoplasty
24	M	61	II	128	A	A	N	N	N	S	Hemicolectomy
25	M	52	II	122	N	N	A	N	N	L	Ureterolithotomy
26	F	78	II	89	A	N	N	N	N	S	Thrombectomy (iliac artery)

TABLE II. *Predictive values of patient characteristics on isoflurane partial pressure ratios (mean values during steady state). No significant (ns) differences could be found for the patient characteristics sex (M* vs *F), position (S* vs *L), FEV_1 (N* vs *A), patient's history (N* vs *A), physical examination (N* vs *A) and chest x-ray (N* vs *A). F = female; M = male; S = supine; L = lateral; N = normal; A = abnormal; α = intercept; β = slope.* RSD *= Residual standard deviation; ANOVA = analysis of variance. n = 26*

Patient characteristic	Uptake $(Pa_{180}/P\bar{E}'_{180})_{20-60}$		Elimination $(P\bar{E}'_{180}/Pa_{180})_{61-120}$		Statistical method
Age (continuous scale)	$\alpha = 0.916$, $\beta = -0.0023$ ($P < 0.01$) $r^2 = 0.262$, RSD = 0 084		ns		Regression analysis
ASA					
I	0.880 (0.065)	$P < 0.01$	ns		ANOVA
II	0.766 (0.080)				
III	0.696 (0.143)				
Weight	(N *vs* A) ns				
N			N = 0.874 (0.109)	$P < 0.01$	ANOVA
A			A = 0.671 (0.115)		
Vital capacity					
N	0.840 (0.072)	$P < 0.001$	ns		ANOVA
A	0.735 (0.088)				

TABLE III. *Linear regression between each of the estimates of* $P\mathrm{a}_{\mathrm{iso}}$ *and the independent variable* $P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ *(during uptake) or* $P\mathrm{E'}_{\mathrm{iso}}$ *(during elimination).* n = *234.* α = *Intercept;* β = *slope.* RSD = *Residual standard deviation*

	Y	*X*	α	β	r^2	*P*	RSD
Uptake	$P\mathrm{E'}_{\mathrm{iso}}-P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	0.756	0.143	0.042	0.0017	0.536
	$P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	1.003	−0.086	0.278	< 0.0001	0.110
Elimination	$P\mathrm{a}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{iso}}$	0.12	0.125	0.127	< 0.0001	0.202
	$P\mathrm{E'}_{\mathrm{iso}}/P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{iso}}$	0.742	0.061	0.056	< 0.0005	0.155

TABLE IV. *Linear regression between each of the estimates of* $P\mathrm{a}_{\mathrm{iso}}$ *and an independent variable* X. n = *234.* α = *Intercept;* β = *slope.* RSD = *Residual standard deviation. All possible equations with* X *being either* $P\mathrm{a}_{\mathrm{CO_2}}-P\mathrm{E'}_{\mathrm{CO_2}}$ *or* $P\mathrm{a}_{\mathrm{CO_2}}/P\mathrm{E'}_{\mathrm{CO_2}}$ *were computed (eight equations), but only those with the smallest* RSD *are shown*

	Y	*X*	α	β	r^2	*P*	RSD
Uptake	$P\mathrm{E'}_{\mathrm{iso}}-P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{a}_{\mathrm{CO_2}}-P\mathrm{E'}_{\mathrm{CO_2}}$	0.591	0.134	0.357	< 0.0001	0.439
	$P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{a}_{\mathrm{CO_2}}-P\mathrm{E'}_{\mathrm{CO_2}}$	0.852	−0.025	0.235	< 0.0001	0.114
Elimination	$P\mathrm{a}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{CO_2}}/P\mathrm{a}_{\mathrm{CO_2}}$	1.449	−1.38	0.190	< 0.0001	0.195
	$P\mathrm{E'}_{\mathrm{iso}}/P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{CO_2}}/P\mathrm{a}_{\mathrm{CO_2}}$	−0.234	1.19	0.263	< 0.0001	0.138

TABLE V. *Multiple regression analysis between each of the estimates of* $P\mathrm{a}_{\mathrm{iso}}$ *and two independent variables* X_1 *and* X_2. n = *234.* α = *Intercept;* β = *slope.* RSD = *Residual standard deviation. All possible equations with the second independent variable* (X_2) *either* $P\mathrm{a}_{\mathrm{CO_2}}/P\mathrm{E'}_{\mathrm{CO_2}}$ *or* $P\mathrm{E'}_{\mathrm{CO_2}}-P\mathrm{a}_{\mathrm{CO_2}}$ *were computed (eight equations), but only those with the smallest* RSD *are shown*

	Y	X_1	X_2	α	β_1	β_2	r^2	*P* (X_1)	*P* (X_2)	RSD
Uptake	$P\mathrm{E'}_{\mathrm{iso}}-P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{CO_2}}-P\mathrm{a}_{\mathrm{CO_2}}$	0.011	0.181	0.139	0.424	< 0.0001	< 0.0001	0.416
	$P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{CO_2}}-P\mathrm{a}_{\mathrm{CO_2}}$	1.153	−0.094	−0.028	0.562	< 0.0001	< 0.0001	0.085
Elimination	$P\mathrm{a}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{a}_{\mathrm{CO_2}}/P\mathrm{E'}_{\mathrm{CO_2}}$	1.474	−1.582	0.151	0.371	< 0.0001	< 0.0001	0.173
	$P\mathrm{E'}_{\mathrm{iso}}/P\mathrm{a}_{\mathrm{iso}}$	$P\mathrm{E'}_{\mathrm{iso}}$	$P\mathrm{a}_{\mathrm{CO_2}}/P\mathrm{E'}_{\mathrm{CO_2}}$	−0.227	0.042	1.133	0.289	< 0.0001	< 0.0001	0.134

and third categories. An abnormal VC was associated with significantly smaller values of $(P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}})_{20-60}$. During elimination, only overweight was related significantly to small $(P\mathrm{E'}_{\mathrm{iso}}/P\mathrm{a}_{\mathrm{iso}})_{61-120}$.

The regression equations and the RSD for each estimate of $P\mathrm{a}_{\mathrm{iso}}$ and for $P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ during uptake and $P\mathrm{E'}_{\mathrm{iso}}$ during elimination are shown in table III. All equations are highly significant. The best correlation was found between the ratio $P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}}$ and $P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ during uptake and between $P\mathrm{a}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ and $P\mathrm{E'}_{\mathrm{iso}}$ during elimination. However, a wide scatter was present in both periods.

There is a significant correlation between the estimates of $P\mathrm{a}_{\mathrm{iso}}$ and the differences and the ratio of the partial pressure of carbon dioxide (table IV). The correlation coefficients and the RSD were in the same range as those shown in table III. Multiple regression analyses show that patient characteristics did not contribute to the overall predictability of any of the estimates of $P\mathrm{a}_{\mathrm{iso}}$.

The best correlation was found using the independent variables $P\mathrm{I}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ and $P\mathrm{E'}_{\mathrm{iso}}-P\mathrm{a}_{\mathrm{CO_2}}$ as predictors for $P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{iso}}$ during uptake, and $P\mathrm{E'}_{\mathrm{iso}}$ and $P\mathrm{a}_{\mathrm{iso}}/P\mathrm{E'}_{\mathrm{CO_2}}$ as predictors for $P\mathrm{a}_{\mathrm{iso}}-P\mathrm{E'}_{\mathrm{iso}}$ during elimination (table V). Compared with single regression analysis, prediction was improved (smaller RSD).

DISCUSSION

When administering inhalation anaesthetics, most clinicians use clinical signs as a guide to depth of anaesthesia [16]. The introduction of inhalation anaesthetic gas analysers into clinical practice [17] should enable the anaesthetist to control the anaesthetic depth by following the end-tidal partial pressure assuming this reflects arterial partial pressure. If, however, the difference between arterial and end-tidal partial pressure is large, measurement of the end-tidal partial pressure may lead to overestimation of the "depth of anaesthesia" during uptake and underestimation during elimination of an inhalation anaesthetic.

In this study, a rapid increase in both $P\mathrm{E}'_{\mathrm{iso}}$ and Pa_{iso} was found initially. There was a significant and persistent difference between $P\mathrm{I}_{\mathrm{iso}}$ and $P\mathrm{E}'_{\mathrm{iso}}$, and between $P\mathrm{E}'_{\mathrm{iso}}$ and Pa_{iso} throughout the 1-h uptake period (figs 1, 2). Elimination was characterized by rapid decrease in Pa_{iso} and $P\mathrm{E}'_{\mathrm{iso}}$ during the first 10 min. Thereafter, Pa_{iso} and $P\mathrm{E}'_{\mathrm{iso}}$ decreased slowly with a variable difference between the two, the ratio $P\mathrm{E}'_{\mathrm{iso}}/Pa_{\mathrm{iso}}$ being < 1 in most instances.

It is unlikely that the differences observed are caused by anaesthetic technique or the result of a methodological or technical error. The baseline anaesthesia consisted of propofol, alfentanil, pancuronium and ventilation of the lungs with 100% oxygen. This regimen guarantees hypnosis [18], analgesia and neuromuscular block, and allows controlled uptake and elimination of isoflurane without interference by nitrous oxide. Accurate measurement of the partial pressure of isoflurane in blood and alveolar air is critical. The coefficient of variation of the gas chromatographic method used is 4.8% [8] and it can be assumed that weighing the vials before and after sampling further improved accuracy.

Hypothermia causes an increase in blood solubility of isoflurane [10]. Because the body temperature of some of our patients decreased considerably, the measured partial pressure was corrected by a factor which was determined in a separate study with five healthy volunteers. The measured data showed a coefficient of variation of 2.8%, which is within acceptable limits and should not cause erroneous measurements of partial pressure, although the influence of factors such as age and PCV on the temperature correction factor cannot be excluded.

Alfentanil or pancuronium are assumed to be present in blood in concentrations in the nanogram range, and thus unlikely to influence the measurement of isoflurane in blood. Propofol is dissolved in a soyabean fat emulsion and continuous administration of 6 mg kg^{-1} h^{-1} (= fat 0.06 g kg^{-1} h^{-1}) could, theoretically, increase the solubility of isoflurane in blood. The rate of removal of soyabean fat (Intralipid) is governed by a first order reaction in the range 5–10% min^{-1} [19]. Even at an infusion rate of up to 25 g h^{-1} in a 70-kg adult, it does not exceed the elimination limits [20], therefore a constant blood concentration may be assumed in this study. The partition coefficient was measured separately before and after administration of propofol in three patients, and was unchanged.

In healthy awake volunteers breathing subanaesthetic concentrations of isoflurane, $Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}}$ is close to 1 [2]. It may be expected that anaesthesia (causing an increase in $\dot{V}\mathrm{A}/\dot{Q}$ distribution [3, 4]) would lead to a decrease in $Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}}$ [21]. Even young, healthy volunteers showed a decrease in the ratio between arterial and end-tidal partial pressures of nitrous oxide [22] and halothane at anaesthetic concentrations [5]. In a more recent investigation, four healthy patients underwent anaesthesia with isoflurane [6]; end-tidal partial pressures were consistently greater than those for arterial blood, the difference being related to the difference between inspired and arterial partial pressures. Unfortunately, no quantitative analysis is provided for this relationship, but visual inspection of figure 4 of that study suggests that there is considerable variability. It was our objective first to quantify the variability of the gradient between $P\mathrm{E}'_{\mathrm{iso}}$ and Pa_{iso} and second to investigate the usefulness and limits of different variables (patient characteristics, difference between inspired and end-tidal partial pressures of isoflurane and difference between $Pa_{\mathrm{CO_2}}$ and $P\mathrm{E}'_{\mathrm{CO_2}}$) in predicting arterial partial pressure.

Not surprisingly, age correlated significantly with $(Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}})_{20\text{–}60}$. Compared with younger individuals, in the elderly, ventilation distribution is less uniform and, therefore, gas exchange less efficient [23]. Airway closure tends to occur above FRC in older patients [24]. Patients with abnormally small VC have significantly smaller $(Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}})_{20\text{–}60}$. Dueck and colleagues [25] studied patients (age > 50 yr, wide range of abnormal pulmonary function) before induction of anaesthesia and found modest increases in pulmonary $\dot{V}\mathrm{A}/\dot{Q}$ distribution with a small shunt fraction (mean 1.3%) before induction. After induction of halothane anaesthesia, severe gas exchange impairment occurred. This was mainly a result of increased shunt (up to 30% of cardiac output), an increase in low $\dot{V}\mathrm{A}/\dot{Q}$ units (up to 47% of cardiac output), or an increased deadspace ventilation ($V\mathrm{D}/V\mathrm{T}$ up to 0.58), or any combination of these. $\dot{V}\mathrm{A}/\dot{Q}$ distribution was not measured in the present study, but we can assume similar changes in some of our patients, which may partly explain the small values of $(Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}})_{20\text{–}60}$.

The mean $(Pa_{\mathrm{iso}}/P\mathrm{E}'_{\mathrm{iso}})_{20\text{–}60}$ of 0.88 for ASA I patients are almost identical with values reported in a study of healthy patients undergoing isoflurane anaesthesia [6]. The significantly smaller values in patients in higher ASA categories probably reflect some degree of impairment of lung function.

The reason for the significantly small values of $(P\text{E}'_{\text{iso}}/Pa_{\text{iso}})_{61\text{-}120}$ in obese patients during elimination is not known. After 1 h of 1% isoflurane administration, the degree of saturation of the adipose tissue is still very small and therefore does not contribute to an increased gradient. It is more likely that the $\dot{V}\text{A}/\dot{Q}$ mismatch induced by anaesthesia takes longer to resolve in obese patients compared with patients of normal weight.

$P\text{I}_{\text{iso}} - P\text{E}'_{\text{iso}}$ (during uptake) and $P\text{E}'_{\text{iso}}$ (during elimination) correlated significantly with the estimates of Pa_{iso} (table III). However, only 4.2–27.8% of the dependent variable are explained by the gradient between inspired and end-tidal partial pressures. The RSD are high and do not allow prediction of Pa_{iso} with a clinically useful probability.

During routine anaesthesia, the gradient between Pa_{CO_2} and $P\text{E}'_{\text{CO}_2}$ is often known to the anaesthetist. Both carbon dioxide and isoflurane have a low blood/gas solubility and cross the alveolar–capillary membrane easily; therefore, we postulated that estimates of Pa_{iso} could be predicted from $P\text{E}'_{\text{CO}_2}/Pa_{\text{CO}_2}$ or $P\text{E}'_{\text{CO}_2} - Pa_{\text{CO}_2}$. The relatively large RSD (table IV) suggest that $\dot{V}\text{A}/\dot{Q}$ mismatch has a different effect on gas exchange of these two compounds. Isoflurane is an inert gas and equilibration across the alveolar–capillary membrane is almost instantaneous, whereas carbon dioxide equilibration is significantly retarded by the nature of transport of that gas in blood (i.e. the slope of the carbon dioxide dissociation curve and the rate at which carbon dioxide participates in various chemical reactions with blood) [26]. This behaviour of carbon dioxide does not influence gas exchange in young healthy, awake men, but may affect gas exchange in areas of high $\dot{V}\text{A}/\dot{Q}$, where isoflurane may be fully equilibrated, in contrast with carbon dioxide. On the other hand, isoflurane has a much greater molecular weight than carbon dioxide, and this causes increased diffusion limitation in the gas phase [27–29]. This may retard equilibration of isoflurane between alveoli and blood compared with carbon dioxide.

The results in table V show a definitive improvement in the predictability of the estimates of Pa_{iso}. However, it is not certain if it is clinically useful to predict the ratio $Pa_{\text{iso}}/P\text{E}'_{\text{iso}}$ within a 95% range of ± 0.17 (which is approximately 2RSD).

There is no doubt that $P\text{E}'_{\text{iso}}$ may considerably overestimate Pa_{iso} (and, therefore, anaesthetic depth) during isoflurane uptake. This error is particularly likely in elderly patients, in patients with low VC, and in patients with high $Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$ and high $P\text{I}_{\text{iso}} - P\text{E}'_{\text{iso}}$ differences. During elimination, $P\text{E}'_{\text{iso}}$ may overestimate Pa_{iso} (and, therefore, recovery), especially in obese patients and in patients with a small $Pa_{\text{CO}_2}/P\text{E}'_{\text{CO}_2}$ ratio.

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EFFECTS OF TRIMETAPHAN ON THE CARDIOVASCULAR RESPONSE TO TRACHEAL INTUBATION

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SUMMARY

In three groups of 10 patients, we have studied the effect on the cardiovascular responses to laryngoscopy and intubation of bolus doses of saline or trimetaphan 0.05 mg kg^{-1} or 0.1 mg kg^{-1} given 1.75 min before the start of laryngoscopy. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. and tracheal intubation was facilitated with vecuronium 0.2 mg kg^{-1}. During anaesthesia, ventilation was assisted or controlled with 1% enflurane and 50% nitrous oxide in oxygen. Patients receiving saline showed a significant increase in mean arterial pressure and rate–pressure product associated with tracheal intubation. These increases following tracheal intubation were less in trimetaphan-treated patients compared with those of the control group ($P < 0.05$). There was no significant difference in heart rate following tracheal intubation between the three groups. These data suggest that trimetaphan may be used as a supplement during induction, to attenuate the hypertensive response associated with laryngoscopy and tracheal intubation.

KEY WORDS

Complications. hypertension. Intubation, tracheal. cardiovascular response, trimetaphan.

Considerable interest has focused on the haemodynamic changes following laryngoscopy and tracheal intubation [1]. Increases in mean arterial pressure (MAP) of 20–50 mm Hg compared with awake control values, and of 35–65 mm Hg compared with preintubation values, have been reported after tracheal intubation [2–5]. Such cardiovascular disturbances may be dangerous in some patients, particularly in those suffering from myocardial or cerebrovascular disease. This stress response may be attenuated by low doses of fentanyl [1], local anaesthetics [1], α- or β-adrenergic blocking agents [1], and calcium antagonists [6, 7]. Vasodilators such as nitroglycerine [8], sodium nitroprusside [4], isosorbide dinitrate [9] and prostaglandin E_1 [10] have been shown also to be effective for this purpose. The present study was designed to evaluate the efficacy of a single rapid bolus dose of trimetaphan in attenuating this response.

PATIENTS AND METHODS

This study was approved by the Human Investigation Committee of Kobe University School of Medicine and consent was obtained from all patients after a full explanation of the study. The present study consisted of two experimental methods based on those used by Stoelting [4] and Mikawa and co-workers [6, 7].

The first part of the study investigated 20 patients (ASA physical status I) to determine the time course and magnitude of arterial pressure (AP) and heart rate (HR) changes following a single rapid i.v. injection of trimetaphan during anaesthesia but in the absence of stimulation produced by intubation. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and the trachea was intubated following vecuronium 0.2 mg kg^{-1}. Anaesthesia was maintained with 1% enflurane and 50% nitrous oxide in oxygen for elective surgery and end-tidal partial pressure of carbon dioxide ($P\text{E}'_{CO_2}$) was measured by Datex Capnometer (Datex, Helsinki, Finland). Ventilation was con-

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trolled to maintain $P\mathrm{E}'_{\mathrm{CO_2}}$ at 4.0–5.1 kPa. Twenty patients were allocated randomly to groups A and B. After AP and HR had stabilized, patients received trimetaphan 0.05 mg kg^{-1} (group A) or 0.1 mg kg^{-1} (group B) as a single rapid i.v. injection. MAP was recorded continuously via a radial artery catheter and HR was calculated from a 15-s portion of the ECG. All measurements were completed before surgical incision of the skin.

The second part of the study was conducted on 30 normotensive patients (ASA physical status I) undergoing elective surgery, and was designed to determine the effect of prior administration of trimetaphan on the cardiovascular responses to tracheal intubation. Based on the previously determined time course of MAP change following trimetaphan, it was predicted that the onset of action of trimetaphan administered 1.75 min before laryngoscopy would occur at the same time as the onset of hypertension produced by laryngoscopy and tracheal intubation.

No patient had received sedatives or antihypertensive drugs. The patients were allocated randomly to three groups of 10 patients as follows: group C received saline i.v. (control group); group D received trimetaphan 0.05 mg kg^{-1} i.v.; group E received trimetaphan 0.1 mg kg^{-1} i.v. Premedication consisted of diazepam 0.1 mg kg^{-1} by mouth 1 h and atropine sulphate 0.01 mg kg^{-1} i.v. 30 min before induction of anaesthesia. The study design is shown in figure 1.

On arrival of the patient in the operating room, a radial arterial cannula was inserted under local anaesthesia for continuous monitoring of MAP. Heart rate was calculated from a 15-s portion of the ECG (lead II). In all patients, after stabilization of AP and HR, 100% oxygen was breathed via a mask for 3 min and anaesthesia was induced with thiopentone 5 mg kg^{-1}, followed by vecuronium 0.2 mg kg^{-1} to facilitate tracheal intubation. Trimetaphan 0.05 mg kg^{-1}, trimetaphan 0.1 mg kg^{-1} or saline (control) was injected rapidly via a peripheral i.v. cannula 1.75 min before starting direct laryngoscopy (15 s after thiopentone–vecuronium). Two minutes after administration of thiopentone and vecuronium, direct laryngoscopy was attempted, and tracheal intubation was completed within 30 s in all patients with the aid of a standard Macintosh laryngoscope blade. All intubations were performed by the first author, who was unaware of the nature of the injection which had been administered.

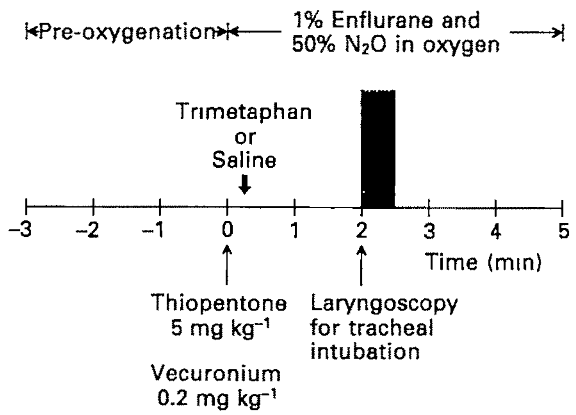

FIG. 1. Schematic diagram of the design of part 2 of the study to examine the effects of trimetaphan on cardiovascular changes following laryngoscopy and tracheal intubation. Shaded area denotes the duration of laryngoscopy and intubation. Trimetaphan or saline was injected 1.75 min before the start of laryngoscopy (= 15 s after thiopentone–vecuronium).

During anaesthesia, ventilation was assisted as required or controlled with 1% enflurane and 50% nitrous oxide in oxygen and $P\mathrm{E}'_{\mathrm{CO_2}}$ was maintained at 4.1–4.9 kPa, measured using a Datex Capnometer by means of a catheter placed in the nostril until after the insertion of the tracheal tube, when sampling took place from a T-piece connector. Serial measurements of HR and

TABLE I. *Patient characteristics (mean* (SEM)). *No significant differences* ($P < 0.05$)

	Part 1		Part 2		
	Group A Trimetaphan 0.05 mg kg^{-1}	Group B Trimetaphan 0.1 mg kg^{-1}	Group C Control (saline)	Group D Trimetaphan 0.05 mg kg^{-1}	Group E Trimetaphan 0.1 mg kg^{-1}
n	10	10	10	10	10
M:F	3:7	3:7	3:7	4:6	4:6
Age (yr)	49.9 (3.3)	46.6 (3.4)	48.2 (3.5)	46.5 (3.1)	50.1 (3.7)
Weight (kg)	57.8 (3.2)	56.4 (3.5)	57.2 (3.0)	58.1 (3.4)	54.3 (3.8)

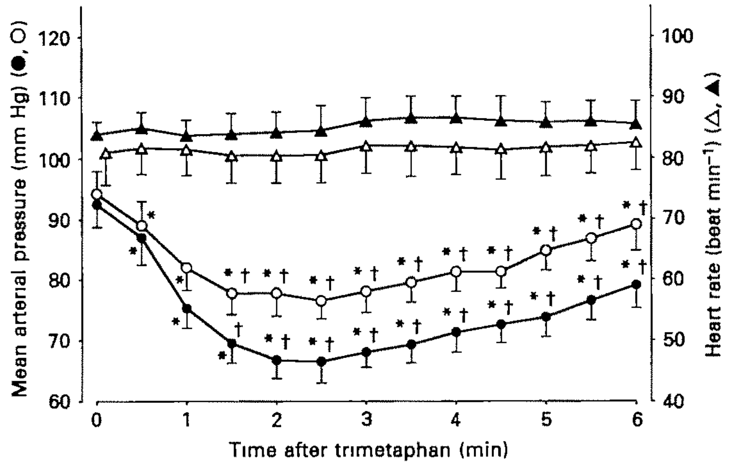

FIG. 2. Changes in mean arterial pressure (○, ●) and heart rate (△, ▲) (mean, SEM) following a rapid bolus i.v. injection of trimetaphan 0.05 mg kg^{-1} (○, △) and 0.1 mg kg^{-1} (●, ▲) without concomitant laryngoscopy for intubation or surgery. There was no difference in HR between the two groups. $*P < 0.05$ *vs* baseline value within group; $\dagger P < 0.05$ for 0.05 mg kg^{-1} *vs* 0.1 mg kg^{-1}.

AP were obtained immediately before induction and 1, 2, 2.5, 2.75, 3, 3.5, 4, 4.5 and 5 min after induction. MAP, HR and the rate–pressure product (RPP) were compared with preinduction (baseline) measurements within the same group and with corresponding measurements among the three groups (groups C, D and E).

Statistical analysis was performed using analysis of variance and Student's *t* test (paired and unpaired). A *P* value of less than 0.05 was considered significant.

RESULTS

The five groups (A–E) of the study were comparable in respect of age, weight and gender (table I). Figure 2 shows the time course and magnitude of MAP and HR changes following a single i.v. administration of trimetaphan 0.05 and 0.1 mg kg^{-1} in patients anaesthetized with enflurane and nitrous oxide in oxygen in the absence of stimulation produced by laryngoscopy for tracheal intubation. MAP began to decrease 30–60 s after administration of trimetaphan regardless of the dose, and the decrease was maximal after 2.5 min, with a return toward control apparent by 4 min (fig. 2). HR did not differ significantly with the two doses of trimetaphan.

There were no significant differences in MAP immediately before the start of laryngoscopy or before induction between the three groups (C–E) (fig. 3). In response to laryngoscopy and intubation, MAP increased significantly in control patients, while the increase was significantly less in the trimetaphan-treated groups. Administration of trimetaphan 0.1 mg kg^{-1} had a greater inhibitory effect on the increase in MAP associated with intubation than the dose of 0.05 mg

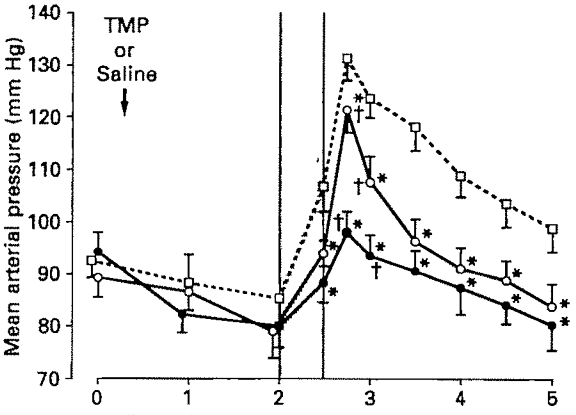

FIG. 3. Changes in mean arterial pressure (mean, SEM) after thiopentone–vecuronium and in response to laryngoscopy and tracheal intubation with trimetaphan 0.05 mg kg^{-1} (○) or 0.1 mg kg^{-1} (●) or saline (control) (□) administered i.v. 1.75 min before starting laryngoscopy. Arrow indicates injections of saline or trimetaphan; dotted area = duration of laryngoscopy and tracheal intubation. $*P < 0.05$ *vs* control; $\dagger P < 0.05$ for 0.05 mg kg^{-1} *vs* 0.1 mg kg^{-1}.

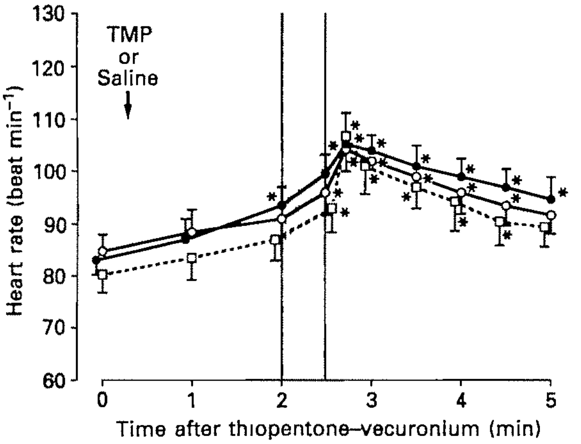

FIG. 4. Changes in heart rate (mean, SEM) after thiopentone–vecuronium and in response to laryngoscopy and tracheal intubation after trimetaphan 0.05 mg kg^{-1} (○) or 0.1 mg kg^{-1} (●) or saline (control) (☐). Arrow indicates injection of saline or trimetaphan; dotted area = duration of laryngoscopy and tracheal intubation. There was no difference between the three groups at any time. *$P < 0.05$ *vs* baseline value within group.

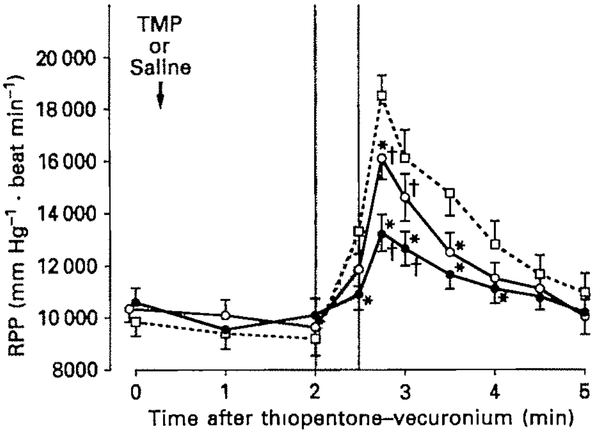

FIG. 5. Changes in rate–pressure product (RPP) (mean, SEM) after thiopentone–vecuronium and in response to laryngoscopy and tracheal intubation after trimetaphan 0.05 mg kg^{-1} (○) or 0.1 mg kg^{-1} (●) or saline (control) (☐). Arrow indicates injection of saline or trimetaphan; dotted area = duration of laryngoscopy and tracheal intubation. *$P < 0.05$ *vs* control; †$P < 0.05$ for 0.05 mg kg^{-1} *vs* 0.1 mg kg^{-1}.

kg^{-1}. Although HR increased after induction and tracheal intubation in all groups, there was no significant difference in HR among the three groups at any time (fig. 4). In contrast, RPP was significantly less in trimetaphan-treated (0.05 or 0.1 mg kg^{-1}) patients compared with the control group after laryngoscopy and intubation (fig. 5). Trimetaphan 0.1 mg kg^{-1} also had a greater inhibitory effect on the increase in RPP following intubation than trimetaphan 0.05 mg kg^{-1}.

There were no abnormal changes in ECG in any patient of the five groups (A–E). No patient required pressor drugs to treat severe hypotension.

DISCUSSION

Trimetaphan has been used to treat hypertensive emergencies and for controlled hypotension during and after anaesthesia [11]. The hypotensive effect is caused by sympathetic block [12]. There is only one previous report on the effect of trimetaphan on the cardiovascular changes following tracheal intubation [13]. In that report, Siedlecki demonstrated that a continuous infusion of trimetaphan 1 mg min^{-1} for 3–9 min blunted the cardiovascular responses to tracheal intubation. However, a single rapid injection is a more practical and simpler method than continuous infusion and is less likely to cause prolonged hypotension immediately before operation.

This study has confirmed previous reports that intubation of the trachea following thiopentone and a neuromuscular blocking agent is associated with significant increases in HR and MAP. In this study, trimetaphan 0.05 mg kg^{-1} and 0.1 mg kg^{-1} was found to attenuate the increases in MAP and RPP compared with those of the control (saline) group. As with other vasodilators which have been reported to have no effect on the increase in HR associated with tracheal intubation, trimetaphan also failed to prevent tachycardia. The maximum mean RPP after intubation in the trimetaphan 0.1 mg kg^{-1} group was 13286 mm Hg·beat min^{-1}. This value is comparable to values of RPP of 17916 mm Hg·beat min^{-1} and 15868 mm Hg·beat min^{-1} in response to intubation in patients given hydralazine and buprenorphine, respectively, before induction [14, 15].

We consider that the decrease in AP after administration of trimetaphan is influenced by three factors. First, existing sympathetic tone. This is illustrated by the fact that AP may be decreased only minimally in recumbent subjects, but may decrease markedly in sitting or standing subjects [11]. Second, because the usual predominant tone at the heart is parasympathetic, the effect of ganglionic block by trimetaphan on the heart causes tachycardia [11] which may minimize the decrease in AP after trimetaphan. Third, the magnitude of the decrease in AP may depend also on circulating blood volume or venous return.

We believe that undue hypotension following trimetaphan may be avoided if sufficient i.v. fluids are given to recumbent patients. In the present study, profound hypotension did not occur in any patient, regardless of the dose of trimetaphan. As shown in figure 2, the onset of action of trimetaphan was rapid, and duration of action was short; therefore, it seems to be an appropriate drug to attenuate the cardiovascular responses to tracheal intubation.

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PSYCHOMOTOR RECOVERY AFTER OUTPATIENT ANAESTHESIA: INDIVIDUAL IMPAIRMENT MAY BE MASKED BY GROUP ANALYSIS

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SUMMARY

Recovery from outpatient anaesthesia with propofol was followed in 10 patients, using a semantic recognition memory test (SemRT) (in a new implementation on a Psion hand-held microcomputer), choice reaction time (CRT) and critical flicker fusion threshold (CFFT). Group analysis of results revealed an effect on psychomotor performance as measured by the SemRT and CFFT (but not the CRT), 30 min after the end of the procedure. Performance on all three tasks had returned to baseline values within 60 min of completing the anaesthetic. Group analysis, however, masks individual impairment which may be clinically important. There was no statistically significant correlation between post-anaesthetic task performance and age, sex, dose of propofol, anxiety or depression score.

KEY WORDS

Anaesthesia outpatient. Recovery. Memory

Tasks of simple and choice reaction time are well established as sensitive methods of evaluating performance in the recovery period following anaesthesia and sedation [1]. However, such tests assess rather basic cognitive processes and leave uncertain whether higher order functions might suffer extended residual impairment. For instance, while choice reaction time (CRT) performance might return to normal within 1 h of termination of anaesthesia, it is conceivable that memory retrieval processes might remain relatively impaired. In other words, a more sensitive test might reveal an otherwise unanticipated impairment.

It is possible to present simultaneously both elements of the above tasks (speeded decision making and memory retrieval) by requiring patients to perform a task of *semantic recognition memory* (SemRT) [2, 3]. Simply, the task assesses the speed with which the individual can access knowledge held in long-term semantic memory about the meaning of words and their relationships in order to make a binary decision. Typically, the computer-generated task follows a routine whereby the patient is presented with a series of phrases, each denoting a category of objects or things (e.g. "four-legged animals"); after the presentation of each category phrase, a test word is presented and the subject is required simply to decide whether the word describes a member of that category: in the case of the example above, the test word *dog* would evoke a "yes" response while *hat* would evoke a "no" response. The subject responds via the computer keyboard which permits measurement of the time taken to make the decision. The decision time represents two processes: the time taken to retrieve relevant information about the test word from long-term memory and the time to decode and perform the appropriate motor response.

It is possible to examine the memory retrieval time in greater detail by taking advantage of the known structure of semantic memory storage in order to vary the difficulty of the retrieval operation. The human semantic memory consists of our knowledge of the meaning of words and their relationships. The great advantage of testing semantic memory is that the subject retrieves information which has been learned and stored over a lifetime, hence avoiding the need to learn material for retrieval within the immediate clinical

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or experimental setting. Within semantic memory, words are conceived as being stored in categories within which the words are stacked in conceptual hierarchies. Thus very familiar and commonly encountered instances of the category (e.g. "four-legged animal"—"dog") are conceived as being of "high dominance" (HD) in the category and are readily retrieved spontaneously as category instances and are recognized quickly as such. In contrast, "low dominance" (LD) words are less common instances (e.g. "ram" or "cheetah" in the context of the example above) and take longer to recognize or recall spontaneously.

The difference in time taken to recognize or recall HD compared with LD words provides a measure of retrieval time in memory uncontaminated by motor response processes. Thus by manipulating the factor of retrieval dominance, one can examine the influence of various agents upon the speed of retrieval from long-term memory.

Previous research has shown that the SemRT is sensitive to changes in alertness or arousal. For instance, the time taken to retrieve LD information gradually reduces as physiological activation increases with diurnal changes in alertness [4]. Loss of sleep results in a deterioration in the speed of accessing LD information [5], and time to retrieve HD words decreases as arousal increases with loud noise stimulation [6].

Given the sensitivity of semantic recognition to changes in arousal, it would seem important to consider if the task might prove useful in assessing impairment of function in the post-anaesthesia period. Despite the above positive findings, application of the task in previous studies relevant to anaesthesia have shown uncertain results. Ghoneim, Hinrichs and Mewaldt reported an overall slowing in semantic classification time following oral diazepam 0.1–0.3 mg kg^{-1}, but no selective effect as a function of retrieval dominance [7]. The lack of selective effect may reflect the authors' choice of HD and LD words which did not differ sufficiently in their dominance values (norms are available which assign numerical dominance values to several thousand words for numerous semantic categories [8]). In other words, the difficulty of the retrieval task may have been slight and insufficient to show drug-induced impairment.

A further methodological difficulty may attach to the negative results of Moss and his co-workers who used an SemRT in a battery of tests to investigate the recovery times from anaesthesia induced with methohexitone and maintained with either halothane or alfentanil [9]. While these researchers found no significant effect of each agent on retrieval from semantic memory, one should note that their patients were not tested until 2 h after the anaesthetic agents had been discontinued. It is therefore conceivable that testing occurred too late to detect initial impairment. The researchers deferred testing because their patients lacked the sensori-motor coordination to perform the task presented by BBC microcomputer.

In this paper we introduce a new method of measuring semantic classification time, using a Psion hand-held computer, and provide data on the learning curve with this system. We also present data from a clinical study where this implementation of the SemRT, and two more commonly used tests of psychomotor function, were used to follow the pattern of recovery from outpatient general anaesthesia in 10 patients.

SUBJECTS AND METHODS

Study of the SemRT in unsedated volunteers to determine the learning curve

Subjects. Ten volunteers participated in the study and each completed a Hospital Anxiety and Depression (HAD) questionnaire before performing the task. The questionnaire assessed seven common symptoms of anxiety and seven of depression. For each question the subject's answer scored 0–3, with the higher score indicating increasing symptoms. The final total for both anxiety and depression score ranges from 0 to 21: a score of 7 or less is normal, 8–10 is a borderline score, and 11 or more suggests clinically relevant anxiety or depression [10]. This standardizes the SemRT data, as anxiety increases arousal and may influence performance [11].

Stimulus materials for the SemRT. Ten context categories were chosen from Battig and Montague's list of category norms which define numerically the "dominance" (frequency in language) of a word when it occurs in a specific context [8]. Examples of these categories include "Is it a colour?", "Has four legs?", and "Is a vegetable?". Associated with each category are 12 test words; six words should generate the answer "yes", and six the answer "no". Of the words which generate the answer "yes", three were chosen as HD test words, and three as LD test words, having mean dominance values of 1.7 and 29.4, respectively. The six words which generate the answer "no" are referred to as "non-category" (NC) test words. For example, in the category "Is it a colour?", "red" is an HD member, "mauve" a LD member, and "spider" a NC member.

The difference in time taken to recall HD compared with LD words provides a measure of retrieval time in memory uncontaminated by motor response processes. Thus, by manipulating the factor of retrieval dominance, one may examine the influence of various agents upon the speed of retrieval from long-term memory.

Task implementation on Psion XP microcomputer. The SemRT programme required the user only to identify and press keys corresponding to "yes" and "no", these being demonstrated by the experimenter in an earlier briefing session. As the Psion keys are small, the system is designed to allow several adjacent keys to respond to "yes" and "no" in order to accommodate subjects with large fingers. Before the SemRT itself, preliminary instructions scroll across the screen, prompted by key presses by the subject. The final message is "Are you ready?—press the "Y" key to go on." At this point the subject positions his fingers over the Y and N keys.

After the subject presses the Y key, the first category is presented, chosen randomly from the memory. After 0.5 s, a test word appears, chosen randomly from the list of 12 words associated with the category. The subject responds to the test word as quickly and accurately as possible. The latency period is measured to an accuracy of 5 ms by the computer. A 0.5-s pause follows each response, during which the screen clears. The task continues until the subject has responded correctly to 10 HD and 10 LD test words. In this process he may respond to a variable number of NC words, usually about 20. The duration of the task depends, therefore, on the performance of the subject, but averages 2 min.

If any individual response time exceeds 3000 ms, the result is withdrawn automatically from the programme's internal statistical analysis, and filed under a separate group called "blocks". The "block" phenomenon was noticed during early trials of this system, where occasionally the subject developed inability to respond, and this required a short time to resolve. This phenomenon has been recorded commonly in serial reaction time performance since the initial observation by Bills in 1931 [12]. The number of blocks during a run is expressed as a percentage of the total number of correct and incorrect keystrokes. At the end of the task, the Psion displays the results, which are stored in a Rampak with the date and time. The information in the Rampak can be transferred subsequently to an IBM-compatible computer for manipulation by word-processing and spreadsheet programmes.

Design. During investigation of the learning curve, the volunteers were tested six times at 10-min intervals. To minimize auditory distraction, they listened to white noise through a set of headphones at a volume adjusted to a comfortable level.

Recovery from general anaesthesia

Subjects. We studied 10 patients (four male) attending for outpatient urological investigation under general anaesthesia. Ethics Committee approval and informed written consent were obtained. Any patient receiving regular sedatives or beta-blockers was excluded. Each patient completed an HAD score questionnaire before operation.

Stimulus material, and test design. In addition to performing the SemRT, each subject was studied using the Leeds psychomotor testing system. This compact portable device measures choice reaction time (CRT) and critical flicker fusion threshold (CFFT) [1].

For CRT, the subject viewed a test board containing a central touch-sensitive button and six other touch-sensitive buttons corresponding to six small lights placed equidistant from the central button. The lights were illuminated randomly, and the subject touched the appropriate button to extinguish the light as soon as it illuminated. Two time intervals are measured: the first from illumination of the light until the subject's finger leaves the central button (the recognition time, CRT-R), and the second the total time from illumination of the light until it is extinguished by the subject. The difference between the two is the motor time (CRT-M), as the distance travelled in all cases is the same. The reaction time was taken as the mean of 20 responses.

TABLE I. *Characteristics of volunteers*

				HAD score				Sixth trial	
No.	Sex	Age (yr)	Time of day	A	D	Occupation	Keyboard familiar?	HD mean (ms)	LD mean (ms)
1	F	48	16·00	6	4	Secretary	Yes	742	661
2	M	29	14:00	6	0	Immunologist	Yes	656	725
3	F	26	16:00	4	0	Nurse	No	506	551
4	F	29	09:30	6	2	Lab. Technician	Yes	521	690
5	F	31	14:40	6	1	Doctor	No	512	621
6	F	30	16:00	3	0	Nurse	No	621	650
7	M	30	12:00	12	4	Pipefitter	No	812	886
8	M	33	15:00	7	3	Lab. Technician	Yes	532	631
9	M	32	11:00	10	7	Doctor	Yes	557	555
10	M	43	14:00	4	5	Medical Physicist	Yes	631	700

It has been suggested that the CFFT is a sensitive test of CNS arousal [1]. The subject viewed a set of four light-emitting diodes set in a square pattern, at a distance of 1 m under consistent light conditions. The frequency of flickering increased slowly until the subject was no longer able to distinguish between intermittent and constant light, at which point he pressed a button to record threshold. The task was repeated with the frequency decreasing until the subject first noticed intermittent light. The subject performed the task twice in each direction, and the mean frequency of the four runs was taken as the score.

Method. Each subject performed the SemRT and the CRT task four times before anaesthesia; the CFFT was measured once before anaesthesia. Each task was performed at 30, 60 and 90 min after the anaesthetic agents were discontinued. While performing the SemRT, each subject listened to white noise through headphones, in order to reduce distraction.

Anaesthetic technique. Each patient was fasted and ASA grade I or II. No premedicant drug was given. Anaesthesia (administered by a non-investigator) was induced with propofol until verbal contact was lost, and maintained with nitrous oxide in oxygen supplemented by enflurane ($n = 8$) or halothane ($n = 2$). The patients breathed spontaneously via a Bain system.

Statistics

The effect of anaesthesia on the psychometric tasks and the SemRT was examined using confidence intervals [13]. For each task the result immediately before anaesthesia was taken as the baseline. The median change from baseline, and the 95% confidence intervals (95% CI) around the median were calculated from the results of the post-anaesthesia tasks using the Wilcoxon one sample test. In order to examine the individual responses to anaesthesia as measured by these tasks, a summary statistic was used for each patient: an "area under the curve" (AUC, arbitrary units) was calculated incorporating change from baseline and time, with the time scale used being 0 (before anaesthesia) to 3 (90 min after anaesthesia).

RESULTS

Learning curve

Characteristics of the volunteers are displayed in table I. The mean response times and 95% confidence intervals for HD, LD and NC words are displayed in figure 1. The learning curve can be seen clearly. Overall, it appears that practice was complete after four sessions.

An overall improvement in score was seen between the first and the second trials, with no further improvement in performance thereafter. Five of the volunteers experienced "blocks" during the first trial, with only one during the second trial, and none thereafter (table II).

Recovery from general anaesthesia

The mean age of the patients studied was 42 yr (range 31–58 yr) and mean weight was 73 kg (range 60–102 kg). The duration of anaesthesia was 5–15 min (mean 7 min), and total dose of propofol used was 1.47–3.08 mg kg^{-1} (mean 2.46 mg kg^{-1}).

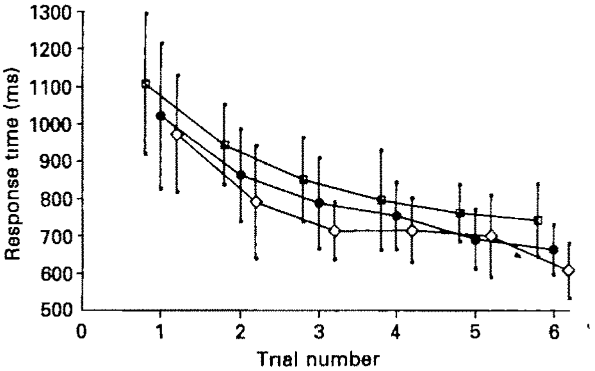

FIG. 1. Mean (95 % CI) changes in response time over six trials with semantic recognition memory test. ◇ = High dominance words; ● = low dominance words; □ = neutral words.

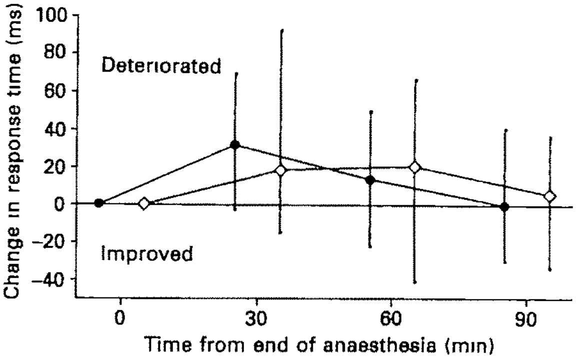

FIG. 3. Median (95 % CI) change in response time from baseline values (0) after outpatient anaesthesia, as measured by CRT task. ● = CRT-Recognition; ◇ = CRT-motor.

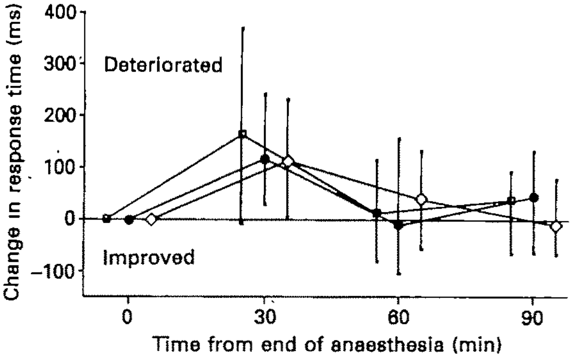

FIG. 2. Median (95 % CI) change in response time from baseline values (0) after outpatient anaesthesia, as measured by SemRT. ◇ = High dominance words; ● = low dominance words; □ = neutral words.

Group analysis

SemRT task. In the initial 30-min period of recovery from anaesthesia, the response times to HD and LD words were increased by medians of 115 ms (95 % CI = 5, 233) and 118 ms (95 % CI = 29, 243), respectively, compared with baseline (pre-anaesthesia) performance (fig. 2). The fact that the CI do not encompass the baseline value of zero would imply significant ($P < 0.05$) impairment at this stage (see [13]). In the case of NC words, the median response time increase of 165 ms is associated with a CI which does encompass the baseline zero (95 % CI = −8, 372).

The fact that the increase in median response time to HD and LD words was identical implies that the anaesthetic had no selective effect as a function of retrieval difficulty. By 60 min, response times to all three classes of words had returned to baseline.

CRT task. At each test period the 95 % CI for change in CRT performance encompassed the baseline value of zero (fig. 3), therefore the slight increase in median response time in the 30–60 min post-anaesthesia period may be considered not significant.

CFF task. In the 30-min period following recovery, the median threshold value and its CI were beyond the baseline zero (fig. 4), implying significant depression of the threshold at this time, although it returned to baseline thereafter.

Individual results

There was considerable inter-individual variation in the performance of SemRT, CRT and

TABLE II. *Score and number of blocks*

	Trial					
Trial	1	2	3	4	5	6
Mean score (%)	90.4	94.8	93.5	97.3	95.6	96.5
Range	71–98	86–100	74–100	88–100	87–100	89–100
No. of volunteers having "block"	5	1	0	0	0	0

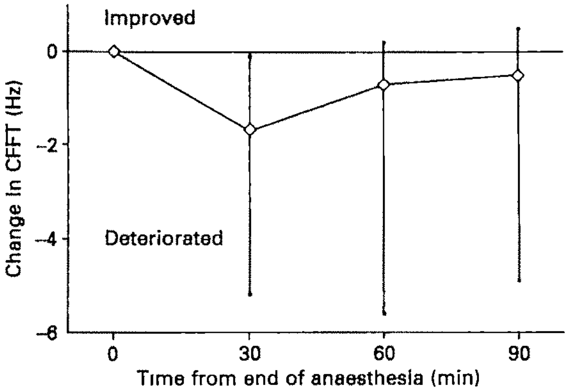

FIG. 4. Median (95 % CI) change in CFFT from baseline value (0) after outpatient anaesthesia.

CFFT tasks following anaesthesia (table III). We could find no statistically significant correlation between post-anaesthetic task performance and age, sex, dose of propofol, anxiety or depression score (Spearman rank correlation test).

DISCUSSION

Group analysis of psychomotor and recovery performance suggests that our anaesthetic technique (essentially, propofol) was associated with return of patient performance to pre-anaesthesia achievement within 60 min of discontinuing the anaesthetic. Examination of the 95 % CI around the median change from baseline suggests that impaired performance was present 30 min after the anaesthetic for SemRT and CFFT, but not for the CRT task. Although the size of the group was small, this was accounted for in calculation of confidence intervals; the data might then suggest that the SemRT and CFFT are more sensitive indicators of post-anaesthetic performance impairment than is CRT testing.

Our results differ slightly from those of a similar study by MacKenzie and Grant, who investigated the postoperative recovery properties of propofol compared with thiopentone and methohexitone [14]. In their study, they detected no significant impairment of psychomotor function measured by CFFT and overall CRT at 30 min following anaesthesia with propofol. The CRT-M, however, was impaired at this time, but had returned to normal by 60 min. Inclusion of the SemRT in the investigation of recovery of higher order mental function in the present study would appear to confirm that this anaesthetic seems to be excellent for outpatients.

The hazards of presenting grouped results in this manner have been discussed recently by Matthews and his colleagues [15]. They observed that presentation of the results as a curve joining means or medians may not be a good descriptor of a typical curve for an individual. When each time point is analysed separately, no account is taken of the fact that the procedure ignores the way in which individuals respond with time: these two factors give a misleading impression of individual behaviour. We also feel that "conventional" analysis of the results may conceal important individual variations. Some of the problems in presenting inter-individual variability adequately in studies of this type have been highlighted by Millar [16]. When assessing "street fitness" after day case anaesthesia, the individual's worst performance is more important than that of a theoretical group. Table III highlights this problem, with the considerable inter-individual variation in performance being obvious from the

TABLE III. *Individual performances as expressed by the "area under the curve" (in arbitrary units) as defined in the text*

Patient No.	HD	LD	Neutral	CRT-R	CRT-M	CFFT
1	−82	252	6.50	21	61	1.75
2	508	−260	580	256	355	−26.95
3	326	−188	−64	−61	226	−7.30
4	164	374	396	−16	5	13.00
5	−232	116	−525	40	13	0.20
6	−302	140	−174	96	−237	−2.65
7	435	675	391	14	50	−4.35
8	212	222	168	28	9	−3.85
9	190	−288	630	130	−13	−1.70
10	335	528	448	−7	66	−1.15

AUC values presented. While the grouped results for these tests show very little effect of the anaesthetic, recovery may be extremely unpredictable, and raises questions about the procedure for discharging patients following day-case anaesthesia (e.g. all patients leave after 90 min). We suggest that each patient requires individual assessment.

Investigation of the postoperative recovery period using psychometric tests helps the anaesthetist to develop a safe outpatient anaesthetic technique, assuming that performance in such tests equates with aptitude for real life skills. This is the subject of continuing debate [16–19]. It should be remembered also that, while impairment in psychometric testing suggests that the patient is not fully recovered, the converse cannot be assumed. We suggest that a further potential hazard may arise when a patient is assumed to be fully recovered simply because he was anaesthetized using a technique which is "known" to have no significant group effect. One postal survey revealed that, despite instructions to the contrary, 73 % of car owners drove within 24 h of outpatient anaesthesia, and 9 % drove themselves home alone [20]. Given this information, the desirability of ensuring complete recovery from drug effects is obvious.

Clearly no single test of psychomotor function can evaluate fully all the facets of patient recovery from anaesthesia and sedation [17]. We feel that the SemRT implemented in this way is a useful addition to the battery of tests already available. It is an indicator of state of arousal [4], providing us with a measure of reaction time and retrieval time, and therefore potentially allows us to quantify effects of drugs on basic and higher order cognitive functions.

In our implementation using the compact, hand-held Psion, we have shown that the task can be used earlier in the period of recovery from anaesthesia than had been expected [9]. The SemRT is learnt easily, with little improvement in response times after four practice runs. Further advantages of the SemRT in this implementation are the ability of the Psion to analyse and store data from the test period, presenting it in a neat and easy to use form, and the fact that, although each test only takes about 2 min to perform, up to 40 responses are obtained, making the data from this 2-min test more statistically viable than would normally be the case.

The implementation has some drawbacks: for example, the small screen and characters demand good eyesight, and the characters, as displayed by the Psion, do not have conventional descenders, which may lead to difficulty. However, none of the present patients or volunteers complained that this was a problem. The small keys may be difficult for some patients, and would certainly be unsuitable for any patient suffering from distal arthropathy. The learning curve demands trial runs before the patient receives any medication, and may delay the patient's procedure. More experience with the system may provide answers to these problems.

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CLONIDINE DOES NOT DELAY RECOVERY FROM ANAESTHESIA

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SUMMARY

Clonidine is known to reduce anaesthetic requirements and improve haemodynamic stability when given as premedication. This study, of 46 ASA I–II patients undergoing thyroid surgery, was designed to assess if clonidine interferes with recovery from anaesthesia. Patients were allocated randomly to three groups to receive, 2 h before surgery, flunitrazepam 1 mg, clonidine 150 µg, or both drugs. Anaesthesia comprised thiopentone, alfentanil, isoflurane and 70% nitrous oxide in oxygen. Recovery from anaesthesia was assessed using a clinical score, electro-oculographic measurements and reaction times to auditory stimuli. Psychomotor tests were performed the day before surgery and 30, 60, 120 and 240 min after arrival of the patient in the recovery room. Psychomotor performance was decreased significantly after operation in the three groups ($P < 0.05$*) and returned to baseline at 240 min. There was no significant difference between the three groups. This study indicates that clonidine 150 µg orally before surgery does not delay recovery from anaesthesia.*

KEY WORDS

Anaesthetic techniques: sedation, psychometric testing. Pharmacology: clonidine, alpha$_2$-adrenergic agonists.

Clonidine, an alpha$_2$-adrenergic agonist, has been used for premedication to improve haemodynamic stability during surgery [1, 2]. It also decreases requirements for anaesthetic agents [3] and induces sleep and sedation in laboratory animals and humans [2, 4]. It follows, therefore, that clonidine premedication might be expected to delay recovery from anaesthesia [2]. The aim of this study was to assess anaesthetic recovery in patients who received benzodiazepine or clonidine, or both drugs, as premedication.

PATIENTS AND METHODS

We studied 46 patients (ASA physical status I or II) undergoing thyroid surgery after informed consent and Ethics Committee approval had been obtained.

Patients with hyper- or hypothyroidism and patients undergoing treatment with beta-adrenergic blocking agents or clonidine were excluded from the study. Patients were allocated randomly to three groups the day before surgery. Two hours before surgery, they received flunitrazepam 1 mg orally (group I), clonidine 150 µg orally (group II) or flunitrazepam 1 mg plus clonidine 150 µg (group III). The anaesthetic procedure was the same for the three groups: induction comprised thiopentone 5 mg kg^{-1} and alfentanil 0.02 mg kg^{-1}; vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with 70% nitrous oxide and 0.6% isoflurane (expired concentration, Multicap, Datex) in oxygen. During surgery, hypertension (systolic arterial pressure > 180 mm Hg) was treated with a 0.01-mg kg^{-1} bolus of alfentanil and hypotension (systolic arterial pressure < 80 mm Hg) was managed by reducing the concentration of isoflurane. Arterial pressure was monitored by an automated oscillotonometer (Dinamap, Critikon) and heart rate by ECG lead CM5.

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Patients were studied on arrival in the recovery room by an independent observer. Recovery from anaesthesia was assessed using simple questions evaluating short-term memory, orientation and cognition (table I).

Psychomotor performance was assessed before and after operation, at 30, 60, 120 and 240 min after arrival in the recovery room, by two different tests. The first test comprised electro-oculography (EOG): the changes in an electrical field, created between periocular electrodes by the movements of the eyes, were measured while the patient was invited to look alternately at one of two pin-shaped white targets fixed to a horizontal line, on a black background, and separated by an angular distance of 10° [5]. Three successive series of 10 to-and-fro movements of the eyes were recorded. In awake patients, jerking movements of the eyes produce rapid changes in voltage which are related linearly to changes in eye movements. A microcomputer converts changes in voltage to velocity of eye movement. The mean value of the peak velocity of 60 jerking movements was calculated for each period of measurements. Oscillations of smaller amplitude have been reported during anaesthesia or after administration of benzodiazepines [5–7].

The second test was based on measurement of motor reaction time (MRT) to 50 consecutive auditory signals, given to the patients by an automatic device at random intervals. The delay between each stimulus and a subsequent manual response (recorded electrically) was calculated.

Results are expressed as mean values (SD). Statistical analysis comprised ANOVA for repeated measures and paired and unpaired *t* tests where appropriate. $P < 0.05$ was considered significant.

RESULTS

The three groups were comparable for patient characteristics, duration of surgery and the doses of anaesthetic agents (tables II, III). Recovery scores were decreased significantly after the end of anaesthesia and these returned to preoperative values 2 h later (table IV). There was no difference between the three groups. EOG showed a decrease in peak velocity of eye movement which was comparable in the three groups (fig. 1, table IV). The mean values of MRT (and the standard deviations) increased after operation in the three groups (fig. 2, table IV).

TABLE I. *Clinical scores*

Vigilance	
Unconscious, not arousable	0
Unconscious, arousable by nociceptive stimuli	1
Unconscious, arousable by verbal stimuli	2
Drowsy	3
Awake, not attentive	4
Awake, attentive	5
Cognition	
No understanding of simple orders	0
Good understanding of simple orders	1
Orientation	
Confused	0
Disturbed	1
Well orientated	2
Short term memory	
Complete amnesia	1
Partial impairment	2
No impairment	3
Evaluation by the patient of his/her condition	
Uncomfortable	1
Comfortable	2
Excellent	3

TABLE II. *Patient characteristics (mean (range or* SD*))*

	Group I ($n = 16$)	Group II ($n = 16$)	Group III ($n = 16$)
Age (yr)	43.5 (27–53)	43.6 (16–69)	42.0 (27–67)
Sex (M/F)	4/12	2/14	4/12
Weight (kg)	66 (12)	62 (13)	60 (10)
Height (cm)	164 (7)	162 (7)	164 (9)

TABLE III. *Anaesthetic requirements and duration of surgery (mean (*SD*))*

	Group I	Group II	Group III
Thiopentone (μg)	32.8 (6.5)	32.7 (8.2)	31.1 (5.1)
Alfentanil (mg)	1.8 (0.5)	1.4 (0.5)	1.5 (0.6)
Vecuronium (mg)	6.7 (1.2)	6.0 (1.2)	6.0 (0.9)
Duration of surgery (min)	104 (24)	96 (20)	115 (55)

DISCUSSION

This study has shown that, with the tests used, premedication with oral clonidine 150 μg did not impair recovery from anaesthesia compared with flunitrazepam.

As the psychomotor tests used to evaluate recovery from general anaesthesia (EOG, MRT) do not improve with practice, they are considered reliable. When used for assessment of "street fitness" after ambulatory anaesthesia, this type of

TABLE IV. *Sensorimotor parameters. EOG = Peak velocity of eye movements; MRT = mean motor reaction time; MRT* SD *= mean value of* SD *of reaction times.* *P < 0.05; **P < 0.01; *intragroup comparisons*

	Before operation	After operation			
		30 min	60 min	120 min	240 min
Clinical score					
Group I	14.0 (0)	9.3 (4.9)**	12.8 (1.8)**	13.6 (0.7)**	14.0 (0)
Group II	14.0 (0)	10.6 (3.4)**	12.3 (3.0)**	13.1 (2.2)**	13.6 (1.5)*
Group III	14.0 (0)	7.7 (5.0)**	12.6 (1.1)**	13.7 (0.6)**	13.9 (0.3)
EOG (deg. s^{-1})					
Group I	266 (52)	135 (58)**	161 (63)**	195 (57)*	216 (51)*
Group II	267 (23)	199 (64)*	189 (54)**	208 (35)*	237 (35)*
Group III	249 (38)	162 (69)**	165 (50)**	190 (63)*	214 (39)*
MRT (s 10^{-2})					
Group I	26.2 (9.0)	39.2 (10.2)*	33.3 (8.5)**	29.8 (7.0)	24.6 (9.0)
Group II	24.9 (5.5)	33.7 (9.5)**	29.8 (11.1)	29.4 (9.6)*	28.3 (7.6)
Group III	22.6 (4.3)	44.4 (13.8)**	33.8 (10.7)**	28.1 (7.1)**	26.4 (9.2)
MRT SD (s 10^{-2})					
Group I	7.1 (5.6)	12.1 (5.2)**	9.3 (5.6)	9.0 (4.5)*	7.3 (5.8)
Group II	6.6 (2.3)	10.1 (4.9)*	8.0 (4.7)	8.0 (4.1)	7.2 (3.6)
Group III	7.8 (9.9)	13.2 (3.0)**	10.7 (3.3)	7.8 (3.1)	5.8 (2.4)

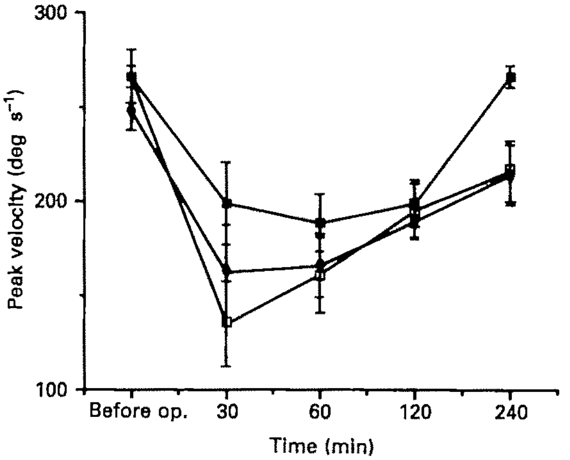

FIG. 1. Mean (SD) values before and after operation, for peak velocity of the electro-oculogram in the three groups of patients. □ = Flunitrazepam (group I); ■ = clonidine (group II); ◇ = flunitrazepam + clonidine (group III). The performances were decreased significantly after operation (see table III), but there was no significant difference between the three groups.

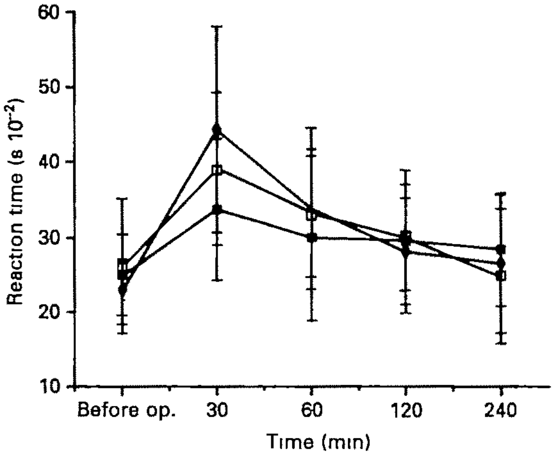

FIG. 2. Mean (SD) values before and after operation, for mean time to response to auditory stimuli in the three groups of patients. □ = Flunitrazepam (group I); ■ = clonidine (group II); ◇ = flunitrazepam + clonidine (group III). The performances were decreased significantly after operation (see table III), but there was no significant difference between groups.

test is usually thought to be too sensitive [8, 9]. In the current study, the sensitivity of these psychomotor tests was an advantage and allowed detection of small differences between groups.

Clonidine did not prolong awakening from anaesthesia in this study although it is known to possess sedative effects. Although recovery has been reported as more rapid after administration of clonidine [1, 2], in both those studies anaesthetic requirements were decreased, and this may explain a more rapid recovery. In contrast, Richards and colleagues reported prolonged recovery after oral premedication with clonidine and propofol–alfentanil anaesthesia [10]. In that study, clonidine was given in a dose three times greater than that used here, and it was administered in combination with a benzodiazepine.

The sedative effect of clonidine is thought to result from an inhibitory effect on spontaneous and evoked activity of central monoaminergic systems involved in modulation of sleep and cortical arousal [11–13]. This effect is mediated by alpha$_2$-adrenergic receptors [14] and is observed after administration of alpha$_2$-adrenergic selective agonists such as azepexole or dexmedetomidine [15–17] and antagonized by alpha$_2$-adrenoreceptor antagonists such as idazoxan [15].

The discrepancy between the well known sedative properties of clonidine and the lack of prolongation of anaesthetic effect noted in this study may be explained by the complex mechanism of action of the drug. For example, the action of clonidine is only partly dose-related, as a ceiling effect has been documented [18]. This effect has been attributed either to an agonist–antagonist action at the alpha$_2$-adrenergic receptor site [19] or to an alpha$_1$-adrenergic agonist action of the drug [20]. Furthermore, a biphasic sleeping time dose–response curve has been documented [4]. In small doses, clonidine produced a small decrease in sleeping time in the rat, whereas doses > 0.1 mg kg^{-1} significantly increased sleeping time [4]. In another study, large doses of clonidine potentiated the effect of inhalation anaesthesia and mimicked the effect of general anaesthesia on electrocortical activity, while a reverse action was reported with small doses [21]. Compared with previous studies [1, 2], we used a small dose of clonidine (about 2 μg kg^{-1}), which has been reported to induce sedation after extradural or parenteral administration [22]. Nevertheless, the hypnotic effect of clonidine may be insufficient to prolong significantly the duration of anaesthesia when compared with a benzodiazepine. However, our study does not exclude the possibility that, in comparison with a placebo or a larger dose of clonidine, significant prolongation of recovery might be demonstrable.

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TOWARDS A STANDARDIZED ANAESTHETIC STATE USING ENFLURANE AND MORPHINE

H. M. ROBB, A. J. ASBURY, W. M. GRAY AND D. A. LINKENS

SUMMARY

General anaesthesia was maintained in 22 patients undergoing major surgery using a proportional-plus-integral control system. The system automatically adjusted the dose of enflurane according to the systolic arterial pressure (SAP). Additional morphine was administered if the system's demand for enflurane exceeded preset limits. In 21 patients, satisfactory control of SAP was achieved and anaesthesia was clinically adequate; no awareness was reported and the mean recovery time was 6.7 min (SD 3.5 min).

KEY WORDS
Anaesthesia · depth.

Despite some inadequacies, clinical signs are the only widely accepted criteria for assessing anaesthetic state, and are used successfully to guide most anaesthetic procedures. However, as their interpretation is subjective, it is likely that the anaesthetic state produced in different patients, although clinically adequate, varies considerably. There is, therefore, no absolute standard for the clinical state of anaesthesia against which new methods designed to measure "depth" of anaesthesia can be assessed.

Our ultimate objective is to develop a system to provide a reproducible anaesthetic state, which automatically makes allowances for between-patient variation, and which might be used to evaluate the different techniques proposed as measures of anaesthetic depth. This system would administer doses of drugs to patients according to their individual requirements, rather than using doses based on a population standard such as MAC. The anaesthetic would be more reproducible than may be managed manually, because the rules would be pre-programmed and not altered. In this study, we aimed to use an automatic control system to standardize the interpretation of, and the response to, one of the clinical signs of anaesthesia. It is not intended that the system in its present form be used for routine clinical anaesthesia.

The earliest report of the use of automatic control techniques during anaesthesia is that of Bickford [1]. Since then, a range of approaches to the automatic control of anaesthesia, and to the central problem of assessment of adequacy of anaesthesia, has been used [2]. In particular, Suppan [3] controlled the administration of halothane, using arterial pressure as an indicator of adequacy of anaesthesia.

The objective of our study was to investigate, first, if one clinical sign, systolic arterial pressure (SAP), could be controlled adequately by a feedback system that manipulated enflurane dosage and prompted the anaesthetist to give morphine, and second if, when SAP is controlled in this way, a clinically acceptable anaesthetic state is produced.

Preliminary results from this study have been reported elsewhere [4].

PATIENTS AND METHODS

We studied 22 ASA I or II patients aged 24–57 yr who were admitted for routine major gynaecological surgery. Local Ethics Committee ap-

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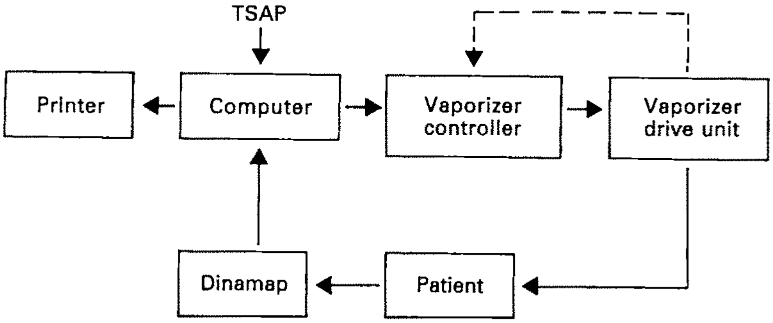

FIG. 1. Arrangement of components in the feedback control system. Arrows show the direction of data flow. The dotted pathway is a loop within the main loop, designed to control the positioning of the vaporizer control knob; this pathway carries analogue data, whereas the others carry digital data.

proval was obtained and all patients gave written consent. Patients with cardiovascular disease, treated or untreated, or taking drugs acting on the central nervous system (except sleeping tablets) were excluded.

The patients were premedicated with ranitidine 150 mg on the morning of operation and temazepam 10–20 mg 1–2 h before operation. Anaesthesia was induced with morphine 0.1 mg kg^{-1} and thiopentone 2.5 mg kg^{-1}, and if the eyelid reflex was still present after 30 s, an additional dose of thiopentone 1 mg kg^{-1} was given. The second part of the sequence was repeated as necessary. Vecuronium 0.1 mg kg^{-1} was then given and the patient's lungs ventilated with a facemask for 90 s with 70 % nitrous oxide and 1 % enflurane in oxygen. The trachea was intubated and the patient transferred to theatre.

In theatre, the patient's lungs were ventilated automatically using a Bain system with a fresh gas flow of 70 % nitrous oxide in oxygen 100 ml kg^{-1} min^{-1}, to provide a compromise between rapid delivery of vapour concentration changes to the patient and a reasonably predictable end-tidal carbon dioxide concentration. Carbon dioxide monitoring was not available, and the fresh gas flow chosen was intended to ensure moderate and consistent hypocapnia [5]. Arterial pressure was monitored non-invasively with a Critikon 1846 Dinamap [6], the cuff being positioned carefully to avoid nerve damage. Enflurane was delivered by Enfluratec 3 vaporizer (Cyprane), modified to allow it to be driven by a stepper motor under computer control (see below). Additional boluses of morphine were given on instruction from the program. Neuromuscular block was maintained with boluses of vecuronium at 30-min intervals. The patients received Ringer's lactate solution 1 litre over the first 1 h, and 500 ml every subsequent 1 h. Blood loss was replaced with extra crystalloid, colloid or blood products as indicated.

Anaesthetic adequacy was assessed clinically according to normal practice. It was assessed also at 5-min intervals using the PRST score [7], which is the sum of individual scores for systolic arterial **P**ressure, heart **R**ate, **S**weating and **T**ears. Each individual score has a value of 0, 1 or 2, giving a possible range for the PRST score of 0–8. A score of 0–4 indicates an acceptable level of response during general anaesthesia.

Automatic control was discontinued approximately 10 min from the end of surgery and no more enflurane was administered. The nitrous oxide was discontinued after the last skin suture or staple was made. Any residual neuromuscular block was antagonized with neostigmine and glycopyrronium. Following the return of spontaneous ventilation and before tracheal extubation, all patients who had not received additional morphine were given a bolus dose of 0.05 mg kg^{-1} i.v. to provide initial postoperative analgesia.

Recovery was considered complete when the patient was able to respond to a request to open the eyes or protrude the tongue.

The anaesthetic procedures were conducted by two of the authors (H. M. R. and A. J. A.); another consultant anaesthetist, who was present throughout the procedure, checked the patient's condition, looking particularly for intraoperative signs of inadequate anaesthesia. All patients were interviewed the following day to establish if they had been aware during surgery.

Equipment

Proportional-plus-integral (PI) control is the most widely used form of automatic control technique [8]. A PI algorithm was implemented on an RML 380Z-D computer which was interfaced to the Dinamap and a vaporizer controller [9]. At the start of the study, a Riken portable interference refractometer was used to check that the output of the vaporizer was within 10 % of the setting at each marked setting, and during the study the output was checked further with a Datex Normac vapour analyser.

The program, written in BASIC, was designed to maintain the patient's SAP at a target value (TSAP), which was 90% of the SAP predicted from age- and sex-standardized tables [10]. The program took data from the Dinamap's memory at 1-min intervals, calculated a suitable output, and adjusted the vaporizer setting. If the Dinamap failed to read a pressure, the most recent valid reading was used.

The system for controlling the vaporizer contained various safety features (fig. 1). The controller interface [9] included independent mechanisms for setting the vaporizer and for sensing its position. The program compared the calculated vaporizer setting with the measured setting; if these differed by more than a preset tolerance of 0.05%, the program returned the vaporizer to the "off" position and then re-set it to the required position. The interface also included a "watchdog" facility to indicate if communication with the computer was lost.

The program controlled the vaporizer setting according to the following rule:

$$\text{Enflurane concentration } (\%) = K_p e + K_i(\Sigma e + I_0)$$

where e is the difference between the actual systolic arterial pressure and the target systolic arterial pressure (SAP – TSAP); K_p and K_i are the proportional and integral gains; and I_0 is a preloaded value for the integral, which is included to shorten the stabilization time.

On the basis of preliminary trials the following settings were made:

K_p set to 0.1 % (mm Hg)$^{-1}$; K_i set to 0.01 % (mm Hg)$^{-1}$.

I_0 set to (120 – (age in years)) mm Hg.

The sum Σe was set to zero at the beginning of each case, and reset to zero when morphine boluses were given.

Two additional rules were incorporated in the control algorithm. First, a minimum concentration of 0.6% enflurane was delivered for the first 10 min. This was to avoid inadequate anaesthesia at the start of surgery; without this rule, the control system might not have administered sufficient enflurane between induction and the start of surgery if the SAP was less than TSAP as the result of induction. The second rule was that, if the sum of five consecutive vaporizer settings exceeded 15%, the controller requested the anaesthetist to give a bolus of morphine 0.05 mg kg^{-1}. In addition, the integral term was reset automatically to its preloaded value. This arrangement could be activated only at 15-min intervals. This rule was designed to emulate the anaesthetist's response to a patient who requires large doses of volatile agent.

TABLE I. *Operations performed. Group B received additional morphine; group A did not*

Operation	Group A	Group B
Hysterectomy and salpingo-oophorectomy	9	8
Ovarian cystectomy	1	—
Uterine myomectomy	1	—
Vaginal hysterectomy, pelvic floor repair	2	—
Reversal of sterilization	1	—

Statistics

The quality of control of SAP in each patient was estimated by calculating the root mean square deviation (RMSD) of the SAP measurements about the TSAP. The RMSD is analogous to the standard deviation but uses the TSAP in place of the mean. Recovery times were used as an additional indicator of the quality of anaesthesia.

The patients were separated into two groups depending on whether the control system indicated that they required additional morphine after induction: group A (14 patients) received morphine only at induction, while group B (eight patients) required at least one additional dose of morphine. The comparison of these groups was considered important, because it might reveal factors which can predict a patient's behaviour before automatic control is started. Intergroup comparisons were carried out with a Mann–Whitney *U* test (two-tailed), and a probability of $P < 0.05$ was considered significant.

RESULTS

Details of the operations are listed in table I.

No patient complained of awareness. The anaesthetic state produced was acceptable to the

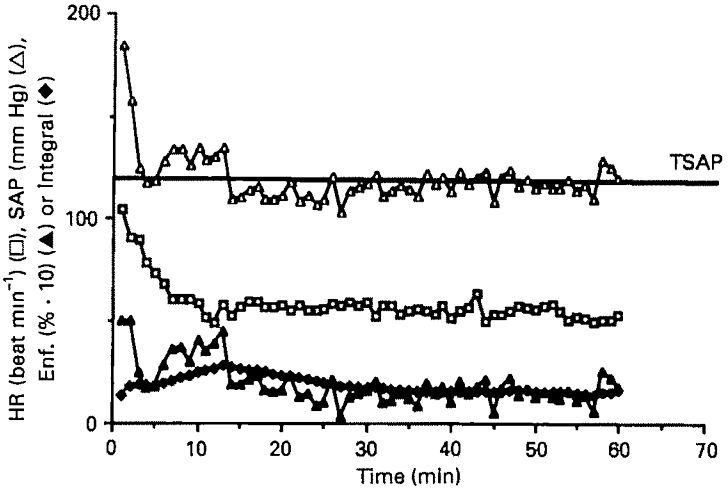

FIG. 2. The pattern of systolic arterial pressure (SAP) (△), heart rate (HR) (□) and inspired enflurane concentration (Enf.) (▲) in a 43-yr-old patient who did not receive additional morphine (group A). The integral (◆) is plotted in arbitrary units. TSAP = Target SAP.

supervising anaesthetist in all but one patient (see below), and this is reflected in the mean PRST score of 0.6, which is in the range designated "light general anaesthesia" by Evans, Bithell and Vlachonikolis [7]. In addition, SAP (mean 118.3 (SD 7.0) mm Hg), heart rate (mean 72.7 (SD 13.5) beat min^{-1}) and rate–pressure product (mean 8640 (SD 1890) mm Hg min^{-1}) were within acceptable ranges. The mean recovery time was 6.7 (SD 3.5) min. All patients indicated that they would accept the same anaesthetic again.

Figures 2 and 3 show traces for typical patients in groups A and B, respectively. The RMSD for each of these patients was close to the mean for the corresponding group. In each case, the actual SAP values were offset from the target SAP by an amount which decreased with time. This is typical behaviour for a PI control system. With some patients, the final steady SAP was reached more quickly than with these patients. The time taken for the offset to reach its final value depends on how well the proportional and integral gains are matched to the individual patient [8].

Figure 2 illustrates the course of events for a 43-yr-old patient undergoing hysterectomy. This patient did not receive additional morphine. The overall control was good (RMSD 6.6 mm Hg). SAP approached more closely to TSAP as the study proceeded and the heart rate settled at about 60 beat min^{-1}. The control algorithm forced the inspired enflurane concentration to follow SAP initially, but the integral term eventually allowed the concentration to stabilize to a value appropriate for that patient. The early increased values of SAP are a consequence of moving the patient in the theatre.

Figure 3 illustrates the data for a 54-yr-old patient undergoing hysterectomy. The overall control was not as good as that depicted in figure 2 (RMSD 11.5 mm Hg). Morphine was given on two occasions, and only after the second did the integral term begin to settle to a value appropriate for the patient. The early SAP swings, related to the transport into theatre, hindered the control by causing a reduction in the integral term.

The system was unable to respond for one patient who required what appeared to be an excessive dose of enflurane in spite of additional morphine. The TSAP was reset at a greater value (thereby breaking the rules for the experimental procedure), and the case proceeded satisfactorily. This patient had an acceptable preoperative arterial pressure of 160/90 mm Hg, but postoperative questioning revealed a history of "previous" hypertension, despite a denial of problems with "raised arterial pressure" before operation. This patient was excluded from subsequent analysis.

For the analysis, therefore, group A contained 14 patients and group B contained seven patients (table II).

There was no statistical difference between the two groups with regard to age, weight, pre-induction arterial pressure, TSAP or total time

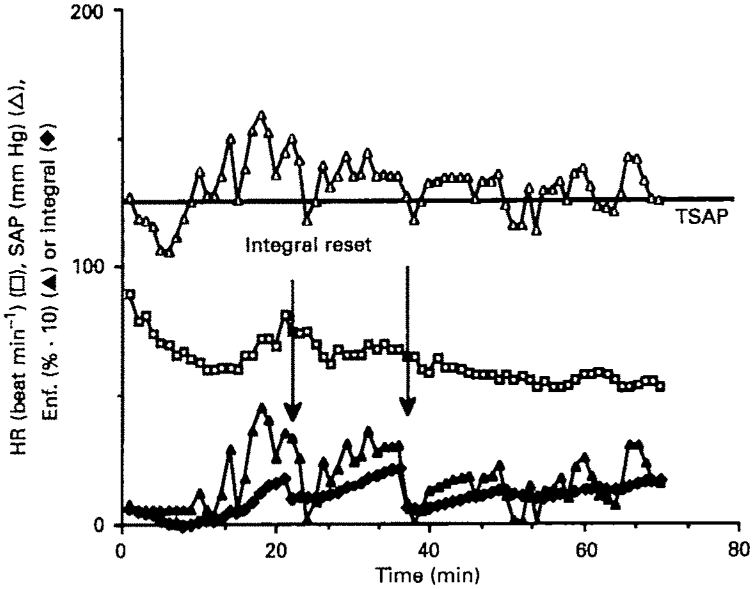

FIG. 3. The pattern of systolic arterial pressure (SAP) (△), heart rate (HR) (□) and inspired enflurane concentration (Enf.) (▲) in a 54-yr-old patient who received additional morphine (group B). The integral (◆) is plotted in arbitrary units. The doses of morphine are indicated by the arrows. TSAP = Target SAP.

TABLE II. *Results for the two groups (mean* (SD) *[range]). TAT = Total anaesthetic time; ATPR = anaesthetic termination to patient response time; TSAP = target systolic arterial pressure; SAP = mean measured systolic arterial pressure;* RMSD *= root mean square deviation; HR = mean heart rate; Enflurane = mean inspired concentration of enflurane; RPP = rate–pressure product; PRST = PRST score.* *$P < 0.05$; **$P < 0.01$ *(two-tailed Mann–Whitney* U *test)*

	Group A (14 patients)		Group B (7 patients)
Age (yr)	41.8 [24–57]		37.6 [25–54]
Weight (kg)	60.8 (12.0) [45–83]		60.7 (11.9) [45–80]
TAT (min)	65.7 (22.9) [47–135]		74.9 (17.3) [45–100]
ATPR (min)	5.1 (1.9) [2–9]	**	10.0 (3.7) [5–15]
TSAP (mm Hg)	117.2 (6.6) [105–128]		114.4 (7.2) [106–126]
SAP (mm Hg)	117.1 (6.1) [106–127]		120.8 (8.6) [111–133]
RMSD (mm Hg)	7.3 (2.2) [4.8–13.3]	**	10.6 (3.4) [6.7–17.6]
HR (beat min^{-1})	67.5 (8.1) [56–84]	*	83.1 (16.7) [62–110]
Enflurane (%)	1.1 (0.7) [0.1–1.8]	**	2.2 (0.4) [1.8–3.1]
RPP	7910 (1070) [6520–10600]	*	10100 (2380) [8220–14200]
PRST	0.46 [0–4]		0.82 [0–4]

from induction to discontinuation of the nitrous oxide. The means of the individual RMSD values for both groups were small, and were significantly different between the groups, being smaller in group A. The mean heart rate, rate–pressure product and inspired enflurane concentration were significantly less, and the mean recovery times significantly shorter, in group A compared with group B.

DISCUSSION

There are two principal conclusions from this study. The first is that, by using the simple PI control system described, it was possible to maintain SAP at a predetermined value in a group of patients undergoing major surgery. The second is that, when SAP was controlled in this fashion, a clinically acceptable state of anaesthesia was produced. This supports the view that SAP may be a major component of the clinical assessment of the anaesthetic state.

The differences in the clinical responses of the two groups are consistent with the differing enflurane requirements that led to the differing patterns of administration of morphine that were the basis of defining the groups. For example, as the basic criterion for additional morphine was that the system was giving a larger than normal dose of enflurane, reflecting a greater difficulty in controlling SAP, it is not surprising that the smaller RMSD was found in group A. The differences in heart rate, rate–pressure product, recovery time and enflurane concentration may be explained similarly. Despite these differences between the groups, anaesthesia was clinically acceptable in both groups.

The use of automatic control techniques in anaesthesia produces a performance that is limited by the quality of the measurement information on which the control is based. The same comment applies, of course, to conventional "manual" control. Hutton and colleagues [6], investigating an earlier Dinamap model than the one that we used, found a high correlation between direct and Dinamap SAP measurements (correlation coefficient = 0.95), although the Dinamap over-read at reduced pressures and under-read at increased pressures. Nevertheless, non-invasive arterial pressure monitors such as the Dinamap are now used widely by anaesthetists.

Although clinical scoring systems have severe limitations, the PRST score is a simple method of quantifying and combining widely used clinical signs. In this study, no patient had a score greater than 4, and the mean values suggest that anaesthesia was adequate, while the recovery times suggest that anaesthesia was not excessive. The greater PRST scores in group B are attributable mainly to the increased heart rate in this group. As group B received greater doses of anaesthetic and analgesic and had longer recovery times than group A, the higher PRST scores in this group probably reflect a drug-related effect, rather than an increase in autonomic activity.

The use of clinical signs (SAP in this case) to guide anaesthetic dosage may be criticized [11, 12], but we would justify this approach on the grounds that the majority of anaesthetists use clinical signs, therefore those signs must contain useful information. This was the approach adopted by Suppan in his pioneering studies [3]. Our study can be seen as an extension of Suppan's work by modern control techniques, which allow not only more precise control, but also more comprehensive evaluation. Furthermore, if a standardized anaesthetic state is to be useful in evaluating techniques of measuring depth of anaesthesia, it must use data which anaesthetists understand and use frequently.

Because anaesthetists use combinations of clinical signs to evaluate the adequacy of anaesthesia, our use of a single controlled variable may be criticized. A single input (SAP)–single output (vapour delivery) system was chosen in the first instance for simplicity and safety. The evaluation of clinical signs (e.g. sweating) often involves a subjective element, and may not give reliable information during some types of surgery; SAP is one of the more common objective clinical signs, can be measured automatically and although it is linked only indirectly to the adequacy of anaesthesia, it nevertheless provides a starting point for a standardized system. Furthermore, a reasonable range of values can be suggested, such as that for natural sleep. Mean arterial pressure might have been a better variable to use, but we rejected it because most anaesthetists do not use this information in day-to-day practice.

The use of a closed loop system rather than an open loop system allows the system to respond to the patient's individual sensitivity to drugs. An open loop system relies on the patient being representative of the statistical population from which the kinetics were derived.

Although the system worked well with the present group of patients, it cannot be expected to work under complex anaesthetic conditions such as those in which there is interference with central control mechanisms, interference with the cardiovascular system or large fluid shifts. The system relies on the fact that the brain is in control of arterial pressure, and that control has not been hindered by the use of beta-blockers or antihypertensive medication.

The target systolic pressure (TSAP) is a crucial part of the system as it effectively sets the depth of anaesthesia. Unfortunately, the choice of TSAP in the individual is difficult, as single measurements of SAP, for example on the ward or in the anaesthetic room, are likely to be unrepresentative because of anxiety, sedation or "white coat hypertension" [13]. For this reason we used age- and sex-related values from tables. A TSAP 90% of that predicted was selected after initial trials suggested that a TSAP of 85% overdosed patients. Our method of selecting TSAP is imprecise, and the group which required additional morphine may have contained those patients whose actual resting SAP were greater than the estimated values obtained from the age- and sex-related tables. Alternatively, some of these patients may have been relatively resistant to the anaesthetic. Repeated preoperative measurements of arterial pressure in a relaxed setting may give a more realistic target value.

A major limitation of this control system, shared by all automatic control systems, is that it can not anticipate changes in surgical stimulation and therefore anaesthetic requirement following such procedures as skin incision. In clinical practice some stimuli can be predicted and dosage increased. The first additional rule in the control strategy (see Methods) provided a background dose of enflurane in anticipation of the start of surgery.

A further limitation is that in some instances the system delivered, for a short time, more enflurane than would normally be given under manual control. In anaesthetic practice it is common to give a bolus of opioid to limit the requirement of volatile anaesthetic, and provide some postoperative analgesia. The second rule, which requested additional morphine, was an attempt to imitate this practice. The resetting of the integral prevented overdose in these patients. This rule, which is based on anaesthetic requirement and not patient response, is not ideal, but as none of the patients took an unreasonable time to recover from the anaesthetic, it seems to have been effective. This study was designed primarily to use computer assistance to control the delivery of a *single* drug, enflurane. We are currently extending the method to control the simultaneous infusion of a short-acting analgesic.

This study should be distinguished from studies using feedback control to deliver volatile agents to produce hypotensive anaesthesia [14]. In these studies the volatile agents produced not only the anaesthetic state, but also the additional depression of the cardiovascular system to effect hypotension. Under these circumstances, the balance between the stimulation caused by surgery and suppression by anaesthesia is tilted in favour of the latter, and hence the normal responses to surgery, particularly the cardiovascular response, are substantially obtunded. A further consequence of hypotension is that the arterial pressure signals are less cluttered with the "noise" of surgical stimulation, and mathematical models can be constructed and used in self-tuning systems. As our system was complicated by the normal cardiovascular responses to surgery, we chose a simple control system to give the best understanding of the process with the maximum patient safety. Furthermore, our non-invasive method of data acquisition, which is appropriate for the majority of clinical cases, did not produce enough information to permit the use of models.

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EFFECT OF PRETREATMENT WITH ORAL PYRIDOSTIGMINE ON SUBSEQUENT ACTIVITY OF ALCURONIUM IN NON-ANAESTHETIZED SUBJECTS

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SUMMARY

We have studied the effects of alcuronium in 10 healthy, non-anaesthetized volunteers after they had been taking oral pyridostigmine 30 mg 8 hourly. The responses of adductor pollicis were recorded using an isolated forearm procedure (IFP) during onset and recovery of neuromuscular block produced by 1.5 mg of relaxant. Previously-noted disparities between mechanomyogram and electromyogram measurement of the first response of the train-of-four (T1) and the ratio of the fourth (T4) to the first response (TOF ratio) were found in most cases, but were unaffected by pyridostigmine. Pyridostigmine did not affect significantly the overall characteristics of neuromuscular block, but repeated IFP after a placebo unexpectedly produced marginally less depression of T1 and more rapid recovery. The hysteresis relationship between T1 and T4 during onset and recovery of block was confirmed, but was not affected by pyridostigmine. Clinically, the results may indicate that pyridostigmine pretreatment is unlikely to have significant effects on the subsequent use of alcuronium.

KEY WORDS

Neuromuscular function: pyridostigmine treatment. Neuromuscular relaxants: alcuronium.

The carbamate anticholinesterase pyridostigmine bromide is familiar clinically in the treatment of myasthenia gravis and as an antagonist to non-depolarizing neuromuscular blocking drugs in clinical anaesthesia [1]. A newer use is as prophylaxis against irreversible acetylcholinesterase (AChE) inhibition by organophosphate (OP) compounds [2]. These are used widely as pesticides and are a hazard of modern warfare. The prophylactic use of pyridostigmine involves taking 30 mg orally 8 hourly to produce approximately a 40% reduction in the body AChE activity. However, this inhibition may produce problems in patients requiring balanced anaesthesia for intercurrent surgery. Given the conventional use of carbamates to antagonize neuromuscular block, the question arises of possible effects of pretreatment on a subsequently administered non-depolarizing blocking agent. A previous study [3] described the use of an isolated forearm procedure (IFP) which allowed the study of the relationship of the first (T1) response of a train-of-four (TOF) at 2 Hz to the fade of the fourth (T4) compared with the first response in non-anaesthetized subjects. This paper reports a further study where the same technique and analysis have been used to study the effects of pyridostigmine on subsequent neuromuscular block produced by alcuronium.

SUBJECTS AND METHODS

We studied male volunteers aged 18–35 yr. All were healthy, with no personal or family history of neurological disorder or allergy and no history of trauma to the forearm. The study was con-

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ducted in accordance with the recommendations of the World Health Organization guidelines for human studies [4]. Smoking and alcohol intake were restricted for 12 h before any experimental session. The response of adductor pollicis to alcuronium 1.5 mg diluted in normal saline 40 ml in the isolated forearm was studied before and after the administration of oral pyridostigmine bromide. The experimental procedure used was identical to that described previously with mechanomyogram (MMG) and electromyogram (EMG) recordings made simultaneously using a Myograph 2000 isometric twitch recorder (Biometer Ltd, Copenhagen) and a Medelec MS6 electromyograph (Medelec Ltd, Old Woking, England) [3]. A fixation period of 3 min was allowed with the cuff inflated after the injection of the neuromuscular blocking drug in the dorsum of the right hand. Recording time zero was taken at the point of injection. Ten subjects were allocated randomly to two groups, either active pyridostigmine or placebo. Each subject was studied during three IFP recorded on study day 1 before taking the drug (IFP1), on study day 2, 2 h after a loading dose of 60 mg (IFP2) and on study day 4, 2 h after taking a final dose of pyridostigmine 30 mg (IFP3). Between the loading and final doses, subjects continued to take pyridostigmine 30 mg 8 hourly. Before each recording venous blood samples were taken for erythrocyte acetylcholinesterase (AChE) analysis using the method of Ellman and colleagues [5].

At each IFP, values were recorded of the first response to TOF stimulation from MMG (MT1) and EMG (ET1) and of the ratio of the fourth to the first response (MT4 and ET4). The ulnar nerve was stimulated supramaximally using stimuli of 0.2 ms duration at 2 Hz. The TOF was repeated at 10-s intervals for 3 min and at 1-min intervals after the release of the cuff up to a maximum of 1 h recording time.

Data in the study were analysed in two ways [6]: comparisons between the three IFP within the active and placebo groups were made using two-way analysis of variance; between-group analysis of the change in response between IFP1 and IFP2, and IFP1 and IFP3 was made using the two-sample *t* test. Results were considered to be statistically significant if $P \leqslant 0.05$.

TABLE I. *Effect of reduction in acetylcholinesterase (AChE) produced by pyridostigmine on neuromuscular block in the isolated forearm in subjects taking active (subjects Nos 1–5) and placebo (subjects Nos 6–10) pyridostigmine. AChE values are of red cell cholinesterase concentration expressed as percentage of individual control value. Neuromuscular block is shown as minimum value of T1 (the first response of the TOF) recorded by MMG ($MT1_{min}$) and EMG ($ET1_{min}$) during three isolated forearm procedures (IFP1–IFP3). Times to minimum responses are shown, together with recovery times to 90% of the control responses. *Blood sample could not be analysed. † Subject was unavailable for recording*

Subject No.	AChE		$MT1_{min}$ (%)			Time to $MT1_{min}$ (min)			Time to 90% MT1 recovery (min)			$ET1_{min}$ (%)			Time to $ET1_{min}$ (min)			Time to 90% ET1 recovery (min)		
	IFP2	IFP3	IFP1	IFP2	IFP3	IFP1	IFP2	IFP3	IFP1	IFP2	IFP3	IFP1	IFP2	IFP3	IFP1	IFP2	IFP3	IFP1	IFP2	IFP3
1	59	56.4	42	26	65	3.6	4.0	3.4	14	14	9	56	37	74	3.8	3.8	3.4	15	18	8
2	60	55.6	2	12	0	4.0	3.4	2.4	24	25	28	13	23	26	4.2	3.4	3.4	22	31	39
3	57.4	54	3	15	3	4.2	3.6	4.4	17	21	29	39	41	12	3.8	3.6	3.3	18	20	39
4	58.5	59.9	33	23	23	3.4	3.2	3.2	24	29	16	34	25	35	3.2	3.4	3.2	26	21	24
5	65.1	69.2	9	30	14	3.2	3.0	3.2	21	23	25	39	28	44	3.8	3.2	3.2	23	25	21
6	104.6	99.6	2	7	0	5.6	4.3	3.0	44	36	50	12	8	6	2.3	3.8	3.0	50	36	50
7	105.7	102.5	40	58	†	4	3.8	†	30	25	†	18	28	†	3.3	3.4	†	30	25	†
8	103.3	100.7	4	20	4	2.2	3.4	4.8	30	26	22	17	20	6	4.2	3.4	4	31	28	23
9	102.3	107	25	40	59	3.8	3.8	3.2	30	20	25	41	70	71	2.8	3.4	3.6	30	17	14
10	103.5	*	2	9	26	3.8	3.8	3.6	33	22	21	11	11	20	3.4	3.6	4.2	29	28	27

TABLE II. *TOF ratios at 50% of (control $T1 - T1_{min}$) during IFP1–IFP3 in subjects taking active pyridostigmine (Nos 1–5) and placebo (Nos 6–10). Paired* t *test analysis shows a significant difference in most cases between values during onset (O) and recovery (R) of alcuronium-induced neuromuscular block measured by both MMG and EMG. Analysis of variance between groups shows no significant effect of pyridostigmine on differential fade. † Subject was unavailable for recording*

Subject No	EMG									MMG								
	IFP1			IFP2			IFP3			IFP1			IFP2			IFP3		
	O	R	O–R	O	R	O–R	O	R	O–R	O	R	O–R	O	R	O–R	O	R	O–R
1	93.8	82.5	11.3	98.1	71.9	26.2	96.3	86.9	9.4	87.5	71.2	16.3	76.5	54.0	22.5	87.5	82.5	5.0
2	97.5	62.5	35.0	95.0	75.0	20.0	95.0	81.0	14.0	80.0	52.5	27.5	82.5	63.8	18.7	67.5	38.1	29.4
3	91.0	73.1	17.9	92.5	78.8	13.7	90.0	50.0	40.0	82.5	43.0	39.5	81.3	55.0	26.3	82.5	43.8	38.7
4	89.0	79.0	10.0	89.0	71.0	18.0	95.0	85.0	10.0	78.0	78.0	0	80.0	74.4	5.6	85.0	72.5	12.5
5	93.8	82.5	11.3	92.5	76.3	16.2	93.0	80.0	13.0	81.0	52.5	28.5	87.5	70.0	17.5	87.5	62.5	25.0
Mean paired diff			17.1			18.8			17.3			22.4			18.1			22.1
SD			10.5			4.7			12.9			15.0			7.8			13.4
P			0.023			0.002			0.040			0.030			0.008			0.022
6	96.3	62.5	33.8	92.5	60.0	32.5	95.0	61.9	33.1	82.5	68.8	13.7	85.0	75.0	10.0	88.8	56.3	32.5
7	90.0	68.0	22.0	100.0	89.0	11.0	†	†	†	79.0	79.0	0	85.0	85.0	0	†	†	†
8	91.3	62.5	28.8	91.3	68.8	22.5	90.0	61.0	29.0	74.4	58.8	15.6	85.5	70.0	15.5	85.6	61.9	23.7
9	100.0	90.0	10.0	97.5	91.0	6.5	98.0	98.0	0	90.0	78.1	11.9	84.0	71.0	13.0	86.3	81.0	5.3
10	89.0	53.8	35.2	91.0	53.8	37.2	92.5	67.5	25.0	81.0	60.0	21.0	79.0	56.9	22.1	81.0	71.0	10.0
Mean paired diff.			26.0			21.9			21.8			12.4			12.1			17.9
SD			10.3			13.3			14.9			7.7			8.1			12.5
P			0.006			0.021			0.061			0.023			0.029			0.064

RESULTS

No abnormal reactions were noted from the use of alcuronium in the IFP and there was no clinically detectable neuromuscular block apart from the forearm after release of the cuff. No subjects taking active pyridostigmine reported any adverse symptoms. Subject No. 7 was unavailable for IFP3 recording for reasons unrelated to the study.

Table I shows the measured red cell concentrations of AChE in subjects taking placebo and active pyridostigmine. The values shown are corrected to a standard PCV of 0.45. There was good agreement between the mean active values for IFP2 and IFP3, showing a 40% reduction in concentration of the enzyme level. The effects of pyridostigmine on alcuronium-induced neuromuscular block were examined by consideration of the maximum block achieved ($T1_{min}$), the time to reach $T1_{min}$ and the period of recovery from $T1_{min}$ to 90% of control T1.

Effects of pyridostigmine on $T1_{min}$

There was wide variation in the degree of neuromuscular block recorded electrically and mechanically in subjects receiving both active and placebo pyridostigmine. Analysis of variance for the placebo group showed evidence of a linear increase in $MT1_{min}$ across IFP1–IFP3 ($F = 5.63$; df = 1, 8; $P = 0.049$). The estimated increase from the mean minimum IFP1 value of 14.6% was 7.4% per session (95% confidence interval (CI) 0.1–14.7%). There was, however, no equivalent significant increase in $ET1_{min}$. There were no significant changes in neuromuscular block in the group taking active pyridostigmine.

Effect of pyridostigmine on time to $T1_{min}$

In subjects taking pyridostigmine there was a small but significant difference in the time taken to reach minimum EMG response between the three IFP ($F = 5.23$; df = 2, 8; $P = 0.035$). In IFP3 the mean time to $ET1_{min}$ was reduced from the IFP1 value by 0.4 min (from 3.7 min to 3.3 min) (95% CI 0.12–0.77 min). In IFP2 the corresponding reduction was 0.28 min (95% CI 0.04–0.60 min). A similar pattern was observed for MMG recordings, but the differences were not statistically significant ($F = 0.86$; df = 2, 8; $P = 0.46$). Analysis between active and placebo groups showed that, for $ET1_{min}$, the differences were significant at IFP3 ($t = 3.8$; df = 7; $P = 0.007$; 95% CI −1.7 to −0.4), but were not significant at IFP2. No differences between groups were significant in the mechanical recordings.

Effects of pyridostigmine on time to 90% recovery

Analysis of variance revealed no significant within-group differences in recovery time between the three IFP for either mechanical or electrical recording. Between the active and placebo groups, there were significant differences for the change between IFP1 and IFP2. The average difference in MT1 recovery time between groups was a reduction of 5.2 min ($t = 6.1$; df = 8; $P < 0.001$; 95% CI 6.2–13.8 min), composed of an increase of 2.4 min in the active group and a decrease of 7.6 min in the placebo. The corresponding difference in ET1 recovery time was an average reduction of 5 min ($t = 2.7$; df = 8; $P = 0.026$; 95% CI 1.4–17.4 min).

Effect of pyridostigmine on agreement between MMG and EMG estimations

The difference between MMG and EMG assessment of relaxation parameters was examined as before [3], by analysis of MT1 – ET1 and MT4 – ET4. In most cases there were negative values of bias. Analysis of variance showed no effect of placebo or pyridostigmine on bias.

Effect of pyridostigmine on differential fade

In almost all recordings in both the placebo and pyridostigmine groups, the relationship between T1 and T4 was a hysteresis. The effect was analysed by taking the T4 value at T1 values during onset (O) and recovery (R) of paralysis which were 50% of control $T1 - T1_{min}$, giving a measure of the effect at the mid-point of the hysteresis curve. Analysis of these values using the paired t test (table II) shows significant differences between mid-range values of T4 for all IFP within the placebo and active groups. Analysis of variance between the groups shows no significant effect of pyridostigmine on the degree of differential fade.

DISCUSSION

The isolated forearm procedure has been shown to be useful in the study of neuromuscular blocking drugs in non-anaesthetized subjects [3, 7]. Although there may be reservations about the relevance of the performance of these drugs in the isolated forearm to whole body response, the technique is valuable in that it allows direct observation of muscle response without interference from general anaesthesia. The present study examined the effects of pretreatment with pyridostigmine on the subsequent actions of the neuromuscular blocker. Administration of these drugs in this unusual sequence is a possibility in modern military anaesthesia because of the use of pyridostigmine as a prophylactic pretreatment against the effects of subsequent exposure to organophosphates. The use of the drug in this way is based on its ability to combine reversibly with a proportion of the end-plate AChE, producing a complex which is resistant to OP attack [2]. After exposure to OP, which causes irreversible inhibition of non-complexed AChE, the pyridostigmine–AChE complex breaks down, effectively providing an enzyme autotransfusion at the postjunctional membrane. Alcuronium was chosen for study because of its established military use [8]. The 1.5-mg dose of alcuronium used in the IFP was sufficient to produce surgical relaxation in most subjects, although there was wide variation and two subjects did not exhibit paralysis to less than T1 = 25%. Pyridostigmine caused a reduction in red cell concentration of AChE to 60% of normal. This degree of inhibition was not associated with any significant change in the value of $T1_{min}$. Corrected red cell AChE concentration is a standard enzyme measure [5], but its exact relationship with end-plate AChE is unknown.

Repeated IFP with placebo showed a small but statistically significant effect on the average mechanical minimum T1 response, with a linear increase through the three IFP. This is the opposite of any predicted carry over of non-depolarizing activity of alcuronium. There was no equivalent change associated with pyridostigmine. There was a small reduction in the time taken to reach $T1_{min}$ within the pyridostigmine group which persisted in the between-group analysis. This finding is the opposite of that predicted if pyridostigmine is acting as an antagonist to alcuronium. Between-group analysis also revealed a small reduction in recovery time between IFP1 and IFP2 because of a reduction within the placebo group. The possibility exists that pyridostigmine itself may be causing a degree of depolarization block, but studies using single fibre electromyography [9] have discounted this possibility at the dosage used in this study.

Our previous study [3] showed that for alcuronium in the IFP there was a significant bias of EMG over MMG values of T1. This has been confirmed by the present study which also showed that the bias was unaffected by pyridostigmine. The differential fade effect of T4 with respect to T1 seen previously was confirmed and there was no detectable modification by pyridostigmine. Two current hypotheses for fade [10] are that block of prejunctional cholinergic positive feedback receptors causes a failure of sustained ACh release, or that the open ion channels become blocked by stearic hindrance by the blocking drug. Bowman [10] has suggested that the rate of attachment of the drug at the prejunctional receptor is slower than that postjunctionally. This leads to a gradual onset of fade as ACh release diminishes. The alternative view is that, as the attachment of ACh to the ACh receptor becomes less secure, the channels are influenced more by ACh, which tends to hold the channels open during the TOF. Molecules of the neuromuscular blocking drug then cause channel block.

The effect of pyridostigmine pretreatment may be considered on both these possibilities. In terms of ion channel blocking, by inhibiting AChE, pyridostigmine may produce an increase in the average concentration of ACh at the postjunctional receptors and increase the average channel open-time. In the presence of relaxant, more channel blocking is likely and fade should occur earlier in the IFP. The differential fade would therefore be expected to disappear after pyridostigmine pretreatment. Alternatively, if pyridostigmine has an equal action at the pre- and postjunctional receptors, there may be increased positive feedback leading to increased ACh release. This should cause the rate of attachment of relaxant to the prejunctional receptor to be slowed, leading to a delay in the onset of fade and a shift to the right of the differential fade loop. The finding that differential fade persists after pyridostigmine may therefore favour the prejunctional mechanism, rather than ion channel block as an explanation.

In conclusion, the study has shown that, in the isolated forearm, pyridostigmine pretreatment produced small changes in the action of a neuromuscular blocking drug. Although extrapolation to the whole body is difficult, these results may indicate that the use of pyridostigmine as prophylaxis against OP poisoning is unlikely to produce significant difficulties with the use of neuromuscular blocking drugs in balanced anaesthesia.

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OPIOID RECEPTORS AND THEIR LIGANDS: NATURAL AND UNNATURAL

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The identification of multiple opioid receptors and the discovery of the opioid peptides in the mid to late 1970s led to an explosion of interest in opioid physiology and pharmacology. Both basic scientists and those in the pharmaceutical industry observed that the development of more selective ligands for these receptors would have enormous therapeutic potential. Ten years later, there have been no therapeutic breakthroughs, many industrial companies have abandoned opioid research and scientific sessions on basic opioid research are often sparsely attended. In this review, the present situation will be summarized and an attempt made to explain why the therapeutic potential for this area of research has failed, as yet, to achieve fruition.

NATURAL LIGANDS

It is now clear that there are three separate families of natural or endogenous peptide opioid receptor ligands: enkephalins, endorphins and dynorphins. They are derived from three different prohormones: proenkephalin [28, 56], pro-opiomelanocortin [55] and prodynorphin [37], which are coded by messenger RNAs derived from three separate genes (fig. 1). The human proenkephalin, pro-opiomelanocortin and prodynorphin genes have enough similarities in their structures to suggest that they have evolved via similar evolutionary mechanisms [34]. However, there is considerable heterogeneity among mammalian genes such that porcine cDNA fails to detect bovine messenger RNA or rat messenger RNA [10]. In a single species, the three families of opioid peptides differ in their distribution [39], receptor selectivity and neurochemical role. The enkephalins and dynorphins are often found to coexist with other neurotransmitters such as serotonin (5-HT) and noradrenaline [11], but the details of how the peptides modulate the activity of the co-transmitter await elucidation.

Proenkephalin family

The first opioid peptides were characterized by Hughes and co-workers as pentapeptides with the structures Tyr-Gly-Gly-Phe-Met (methionine enkephalin ([Met]enkephalin)) and Tyr-Gly-Gly-Phe-Leu (leucine enkephalin ([Leu]enkephalin)) [35]. The precursor, also known as proenkephalin A, was demonstrated to have these two peptides in a fixed ratio of six [Met]enkephalin sequences to one [Leu]enkephalin, although some of the [Met]-enkephalin sequences may incorporate several more amino acids to produce larger opioids. Proenkephalin-containing cells are spread widely throughout the brain and spinal cord and in more peripheral sites such as the adrenal medulla and gastrointestinal tract.

Pro-opiomelanocortin family

Pro-opiomelanocortin (POMC) is a multifactorial prohormone which is the common precursor of the opioid beta-endorphin and the non-opioid hormones adrenocorticotrophic hormone (ACTH) and alpha- and beta-melanocyte-stimulating hormones [74]. As the [Met]enkephalin enkephalin sequence is found at the amino terminal of beta-endorphin it was originally assumed, incorrectly, that [Met]enkephalin was derived from this source. No [Met]enkephalin is derived from POMC. The term endorphin is reserved for those opioid peptides which are derivatives of POMC. The name of an opioid peptide is often followed by a number to denote the number of amino acids in the sequence; beta-

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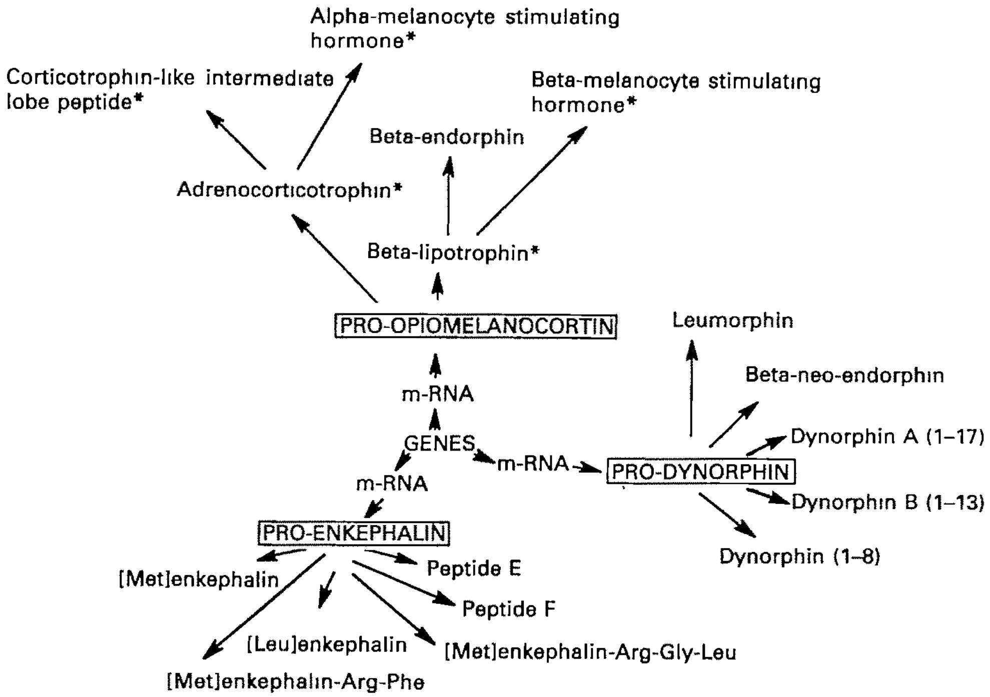

FIG. 1. Opioid peptides and their precursors. *No opioid receptor activity.

endorphin for example may be termed beta-endorphin (1–31). Whilst the pituitary gland is the major site of POMC biosynthesis, POMC is found also in limited areas of the brain such as the hypothalamus [74] and in the periphery.

Prodynorphin family

Prodynorphin, which was known as proenkephalin B, contains [Leu]enkephalin sequences but no [Met]enkephalin sequences. The opioid peptides derived from this precursor include the dynorphins, beta-neoendorphin and leumorphin [36], all of which contain the [Leu]enkephalin sequence at the amine terminus. Prodynorphin, in common with proenkephalin, is synthesized throughout the CNS in a wide variety of neuronal systems [39]. The distributions of dynorphin and enkephalins are often contiguous and they may participate via separate receptors in related CNS functions. In common with the enkephalins, the prodynorphin family are found also in peripheral tissues.

OPIOID RECEPTORS

The original classification of opioid receptors into mu, kappa and sigma [51] was based on the activity, in the chronic spinal dog, of three unnatural (or at least exogenous) ligands: morphine (mu), ketocyclazocine (kappa) and SKF 10047 (N-allylnormetazocine) (sigma). Subsequently, the delta receptor, to which [Leu]enkephalin binds preferentially, was added. This receptor is particularly abundant in the mouse vas deferens [44], a preparation which was one of the models used by the Kosterlitz group to characterize opioids and their receptors.

The final Greek letter used to annotate opioid receptors was epsilon. This receptor, described originally in the rat vas deferens [86], is sensitive to beta-endorphin (1–31) but not to morphine, whilst kappa receptor agonists are antagonists at this receptor type.

Naloxone has antagonist properties at all opioid receptors, but it antagonizes mu receptor activation in a smaller concentration.

Of the above receptors, opioid binding sites are now firmly recognized for only three classes (mu, kappa and delta), although there is some evidence for further subdivisions of the kappa and mu sites (see later). What happened to the sigma and epsilon receptors will be discussed at the end of this section. Much of the speculation alluded to in the following section will be answered only when the detailed structure of the opioid receptors is described. The disclosure of this structure, which is the subject of intensive study in at least three laboratories, has been expected imminently for the past 5 years!

Mu receptors

Whilst products from all three opioid genes have affinity for this receptor, no selective natural ligand has been isolated. In contrast, the dynorphins have selectivity for kappa receptors and [Leu]enkephalin has selectivity for delta receptors. It may be that the mu site is a "universal" opioid receptor [2], or that a mu receptor selective ligand has yet to be discovered. As many of the therapeutically used exogenous ligands such as morphine do have selectivity for the mu site, it is interesting to note that several molecules with chemical structures similar to morphine have been found in mammalian brain [14]. It is not certain if these molecules have been derived from dietary sources or if they are synthesized in the brain. The opioid antagonist naloxone does not have great selectivity for mu receptors, and this has hindered attempts to study the physiological and pharmacological role of this binding site (see later for further discussion). However a 14-OH codeine derivative, cypridime, has been described as having consistently mu-selective properties both in *in vitro* binding assays and in *in vivo* analgesic testing [30]. Further work with this compound, if it is truly a selective mu antagonist, may clarify the situation.

Based on the results of the radioligand binding studies, Pasternak has suggested the existence of mu receptors in two affinity states, the high affinity state being designated mu_1 and the low affinity state mu_2 [59]. Using an antagonist thought to be selective for the mu_1 site (naloxonazine), it was suggested that opioid analgesia, but not respiratory depression, was associated with the mu_1 site [43]. Subsequent work by the same group suggested that mu_1 receptors mediated supraspinal analgesia, whilst mu_2 receptors had a role in spinal analgesia [61]. However, the existence of mu isoreceptors has been questioned by others [66, 69]. Mu opioid receptors are distributed widely and the sites are most dense in regions of the brain associated with pain regulation and sensorimotor integration [50].

Delta receptors

Most of the products of proenkephalin, particularly [Leu]enkephalin have selectivity for this receptor type. In contrast the opiate alkaloids have low affinity [60]. The enkephalins themselves are degraded very rapidly, but more stable derivatives such as D-Ala^2-D-Leu^5-enkephalin (DADLE) have been utilized as selective delta receptor agonists. Most delta receptor antagonists are peptides related to the enkephalins (e.g. ICI 174864) [29] and thus present problems with respect to administration and penetration to their site of action *in vivo*. In view of this, studies of physiological and pharmacological responses to delta receptor activation using such antagonists are open to question. Naltrindole, a highly specific non-peptide delta antagonist which is active after peripheral administration [63], may provide a more satisfactory tool for these investigations.

Delta receptors are distributed less widely than mu receptors and are located most densely in neural areas involved with olfaction and motor integration [50].

Associations between mu and delta receptors

As early as 1981, evidence was presented that mu and delta receptors were capable of interconverting [6]. Two years later, the idea of a complex allosteric receptor was proposed [4], in which the affinity of the receptor for various ligands is controlled by the presence or absence of regulatory substances such as guanosine triphosphate and cations such as Na^+ and Mg^{2+}. In a study of anticonvulsant activity, Tortella, Robles and Holaday observed that mu and delta receptors appeared to be coupled, in that activation of one receptor changed the affinity of the other [80] (a similar phenomenon is seen with the benzodiazepine and gamma aminobutyric acid (GABA) receptors). Both mu and delta receptors appear to be coupled to potassium channels [2] and are coupled to similar signal transducing, guanine nucleotide binding proteins (G proteins) [30], although attempts to purify the receptor proteins have revealed slightly different molecular masses for the two receptor types. A possible explanation for the apparent association of the two receptors, together with their differing anatomical distribution, may be that both mu and delta receptors can exist in two forms either complexed together or separate (non-complexed) [31, 65]. It is possible that the two states of the mu receptor might correspond to the mu_1 and mu_2 isoreceptors described earlier.

Kappa receptors

Most of the products of prodynorphin interact with kappa receptors. Whilst [Leu]enkephalin has selectivity for delta receptors, any extension of the molecule results in loss of delta activity. Progressive increases in the length of the peptide increase the potency of the molecule at kappa binding sites. Whilst dynorphin (1–13) and dynorphin (1–17) (often termed dynorphin) are the most potent peptides with respect to kappa binding and pharmacological assay systems, some of the shorter peptides such as [Leu^5]enkephalin-Arg^6-Arg^7-Ile^8-Arg^9 (dynorphin (1–9)) are more selective [60]. A highly selective kappa receptor antagonist, nor-binaltorphimine, has now been described [78] and its use is already allowing some reappraisal of the role of kappa receptors in opioid pathways and the activity of opioid drugs (see later). There is clear evidence that kappa receptors are separate from mu and delta receptors as, unlike the latter, kappa receptors are coupled with calcium channels [2] and have no affinity for mu or delta agonists. Binding studies have suggested at least two kappa binding sites and the evidence for these kappa$_1$ and kappa$_2$ sites has been increased by the demonstration of differential binding of kappa agonists to these two sites. Furthermore, the distribution patterns of the two receptors in rat brain are clearly different [89]. Leumorphin, for example, is a kappa ligand, but it has effects on sexual behaviour which are not seen with other dynorphins [36]. It is not clear if this reflects receptor or kinetic differences.

Kappa receptors are located mainly in brain areas associated with pain perception (e.g. periaqueductal grey) and regulation of water balance and food intake [50].

Sigma receptor

Whilst the possibility of there being two sigma binding sites, one sensitive to naloxone and the other not, has been discussed [9], it is generally accepted that most of the pharmacology exhibited by sigma agonists is not naloxone sensitive and thus, the receptor is not "opioid" in nature. It has been suggested that the non-opioid sigma receptors may be identical to the phenylcyclohexyl piperidine (PCP) receptor which binds phencyclidine and related drugs [88], of which ketamine is used clinically in the U.K. However, although both sigma ligands and PCP ligands can displace each other, the order of ligand selectivity differs for the two binding sites [64]. It is not clear if either of these sites mediates the characteristic psychotomimetic action of these two classes of drugs, although it is interesting to note that some classical antipsychotic drugs have a high affinity for the sigma site. The PCP receptor appears to be coupled to the N-methyl D-aspartate (NMDA)–L-glutamate receptor complex, and drugs such as ketamine antagonize allosterically the excitatory transmission mediated by glutamate. As an aside to the above discussion, it has been reported that dextromethorphan, a non-opioid antitussive agent, could be an antagonist at sigma receptors. It has anticonvulsant and neuroprotective properties and its binding sites may be coupled to the phenytoin recognition site [79].

Epsilon receptors

No epsilon receptors have been detected with any degree of certainty in any tissue except the rat vas deferens. Even in this tissue, the varying sensitivity of the preparation to the opioid agonists, compared with other isolated tissues, may not be indicative of a novel opioid receptor. It has been proposed that the differences may be a function of the intrinsic activity of the opioid (morphine having some partial agonist properties at mu receptors) together with the absence of spare receptors in this rat preparation, such that only full agonists such as beta-endorphin (1–31) produce a response [52]. Nevertheless, it has been demonstrated that seizures produced by intraventricular administration of beta-endorphin (1–31) are not antagonized by naloxone or selective delta receptor antagonists [7]. Whilst this is suggestive of epsilon receptor activation, the absence of selective antagonism to beta-endorphin precludes conclusive proof. Beta-endorphin (1–27) has been claimed by Suh and Fu Tseng to be a selective epsilon receptor antagonist [76]. Using this as a tool, they have produced evidence that beta-endorphin (1–31) produces its analgesic effects via the epsilon receptor in mice.

PHYSIOLOGICAL AND PHARMACOLOGICAL RELEVANCE OF MANIPULATIONS OF THE OPIOID SYSTEMS

Analgesic activity

Opioids can modify the response to pain at both spinal and supraspinal levels, and locally in the periphery. Within the CNS, the receptor most commonly associated with pain relief is the mu receptor although, as noted above, Pasternak's group have associated mu_1 receptors with supraspinal analgesia and mu_2 receptors with spinal analgesia [61]. Mu antagonists, selective or non-selective, antagonize the analgesic actions of most natural and unnatural opioid ligands. This does not exclude the possibility that other opioid receptors are involved in pain pathways.

Martin's original classification of opioid receptors [51] ascribed spinal analgesia to kappa receptor activation. In animal experiments, it has been reported that selective kappa agonists are active in tests utilizing chemical irritation as the noxious stimulus, but they are not active in tests using radiant heat as the noxious stimulus [81]. The site of this differential effect is mediated apparently by spinal kappa receptors [70], thus validating Martin's original hypothesis. However, this specificity for a particular modality of pain has been disputed by Shaw, Rourke and Burns, who claim that the analgesic activity of kappa agonists depends upon the intensity of the stimulus rather than its modality [72]. Indeed, Shaw's group concluded that partial agonism or mixed agonist–antagonist activity might be more important than receptor selectivity in explaining the observed differences between analgesic agents.

Using intrathecal administration of dynorphin (1–17), antagonism of morphine-induced analgesia was observed in unpretreated rats, but potentiation of analgesia was demonstrated in morphine tolerant rats [71]. Whilst these results were discussed in terms of kappa receptors being involved in tolerance, it may be that dynorphin is associated with antanalgesic activity under normal circumstances. Both the selective kappa antagonist nor-binaltorphimine and dynorphin antibodies enhance morphine-induced analgesia [24]. Animal experiments with selective kappa agonists may have confused paralysis with analgesia! Certainly, all kappa agonists that have analgesic activity in man also have significant mu agonist activity. Interestingly, evidence is accumulating that morphine itself may decrease rather than increase descending inhibition of nociceptive input at the spinal cord level thus reducing, by an indirect mechanism, the analgesic activity evoked by direct mu receptor activation in the brain and spinal cord [1].

Whilst initial studies did not associate selective delta receptor activation with analgesia, later work had suggested that delta receptors may play an important role in modulating the response to pain. DADLE binds to delta receptors with an affinity nine times that of morphine, whilst its affinity for mu receptors equals that of morphine [85]. Intrathecal administration of DADLE has been demonstrated to be analgesic in patients tolerant to morphine [54]. Furthermore, animal experiments have demonstrated that selective delta antagonists may reverse the analgesic action of delta but not mu agonists [32]. Thus it seems likely that analgesia can be mediated by both mu and delta receptor activation at supraspinal [32] and spinal [13] levels. It is possible that these actions involved the mu–delta receptor complex described earlier [31], and that combinations of mu and delta agonists might produce analgesia with reduced side effects [57].

In a series of papers in the late 1970s and early 1980s, Ferreira's group in Brazil described a peripheral action of opioids in antagonizing prostaglandin-induced hyperalgesia [17–19]. This appeared to be mediated by another, hitherto undescribed opioid receptor [16]. These findings prompted the development of quanternary opioid derivatives and their testing as potential peripheral analgesics [15]. Whilst these findings remained an interesting curiosity for some years, recent studies in Germany and France have confirmed the effectiveness of opioids in inflammatory pain [38, 58] and have suggested that peripheral opioid receptors mediating analgesia may be the target for endogenous opioid peptides such as beta-endorphin released during stress [58]. Opioids may both suppress and activate various aspects of the immune system [20] and these factors may be relevant to their peripheral activity in inflammatory pain.

Respiratory depression

[Met]enkephalin is found in relatively high concentrations in the respiratory control areas of the medulla and enkephalins are associated with peripheral chemoreceptors [47]. Whilst this is suggestive of a role for opioid peptides in respiratory control, the effects of naloxone on respiration are equivocal. Although it is a respiratory stimulant in the neonate, it has no such effect in adults. It may be that natural opioids are important modulators of respiratory control only in the neonate [41]. In the adult, they appear to be important only in stress situations.

Nevertheless, in humans of all ages, opioid analgesics cause an increase in arterial $P\text{CO}_2$ and a decrease in Po_2 and pH indicative of respiratory depression. This is caused by reduction in sensitivity of neurones in the brainstem to carbon dioxide [21]. However, a peripheral component may also be important, as stimulation of pulmonary type-J receptors by morphine results in apnoea associated with bradycardia and biphasic changes in arterial pressure [84]. Respiratory depression produced by opioids is usually undesirable and potentially fatal. Thus it was one of the hopes of scientists probing the complexities of opioid receptors and their ligands, that an opioid analgesic might be developed that was free from respiratory depressant activity. The quest began with great promise. Naloxone was shown to be a more effective antagonist of the analgesic activity of morphine than of its respiratory depressant effects [45], suggesting that the two properties of morphine were mediated by separate receptors. Subsequently, other workers have confirmed a separation between analgesia and respiratory depression [43, 62]. However, the methods used are open to criticism and the result obtained could have alternative explanations [87]. Which receptor mediates respiratory depression? Of the three main receptor types, there is the least evidence that kappa receptors are involved in respiratory depression, although a modulatory role in some aspects of respiratory control has been suggested [87]. However, the prospect that a very selective kappa agonist might be the drug of choice is unlikely, in view of the debatable analgesic effect of kappa receptor activation (see above). Furthermore, it appears to be difficult to separate dysphoria and psychotomimetic activity from compounds of this type.

As mentioned above, Pasternak's group associated analgesia, but not respiratory depression, with activation of mu_1 receptors [43]. Meptazinol has been identified as an opioid analgesic with mu_1 selectivity [75] and, as if in confirmation of Pasternak's hypothesis, it has been shown to have significantly less effect on respiration than equi-analgesic doses of morphine [26]. However, meptazinol has significant cholinomimetic properties [5] and co-administration of atropine with meptazinol reveals respiratory depressant activity [12]. The emergence of a high incidence of vomiting with meptazinol (as might be expected as opioids stimulate the chemosensitive trigger zone and cholinomimetic drugs stimulate the vomiting centre) has led to a loss of interest in this agent both by prescribing doctors and by the company concerned. There is still controversy over whether or not mu or delta receptors, or both, are involved in respiratory depression. Ward and Takemori [82] observed that the apparent involvement of various receptor types depended upon the methods used to measure respiration, mu receptors being involved if the animal was stressed during the experimental procedure. Other work has suggested that mu receptors mediate a reduction in tidal volume, whilst delta receptors mediate a decrease in ventilatory frequency [53]. Both mu and delta receptors are located in areas of the brain responsible for respiratory control [68]. It has been suggested that the mu–delta receptor complex mentioned earlier is important in the control of respiration. Occupation of the mu receptor site might be a prerequisite to delta receptor-related respiratory depression [23]. In the dog, relatively selective delta receptor antagonists reverse fentanyl-induced respiratory depression with no effect on analgesia [23]. Although this may be a fruitful area for further investigation, it must be remembered that delta receptor activation may also contribute to the analgesic effect.

An interesting aside to the above studies is that the ratio of analgesic activity to respiratory depressant activity, in volunteers, appears to be greater for sufentanil than for fentanyl [3] (i.e. sufentanil produces less respiratory depression per increment of analgesia). Both drugs are classified as "pure" mu agonists.

Cardiovascular system

Systemic administration of morphine produces orthostatic hypotension, mainly via an action on opioid receptors in the central nervous system [67], although a component of the bradycardia and hypotension may be mediated by peripheral type-J receptors located in the alveoli of the lung [83]. The receptors mediating hypotension in the brain are believed to be located on the dorsal surface of the medulla, because topical application of naloxone to this site prevents this response to morphine [47]. Naloxone can attenuate the hypotension which occurs in shock of various aetiologies [33]. In this instance, naloxone appears to be preventing delta receptor activation by natural opioids released during shock. In other circumstances, such as attenuation of the baroreceptor reflex, mu receptor activation appears to be more important [67].

Application of opioids to other parts of the

TABLE I. *Opioid receptors and their ligands. ? = Either existence or specificity is controversial. DADLE = D-Ala^2-D-Leu^5-enkephalin*

Natural ligands	Opioid receptors	Unnatural ligands	
		Agonists	Antagonists
Beta-endorphin [Met]enkephalin (not selective)	Mu	Morphine Fentanyl group	Cypridime
	Mu$_1$?	Meptazinol?	Naloxonazine?
	Mu$_2$?		
[Leu]enkephalin	Delta	DADLE	ICI 174864
Dynorphins, particularly (1–8) and (1–9) leumorphin	Kappa	Ketocyclazocine (not very selective)	Nor-binaltorphimine
	Kappa$_1$?		
	Kappa$_2$?		
Beta-endorphin (1–31) agonist	Epsilon?		
Beta-endorphin (1–27) antagonist?			
	Sigma?	N-allylnormetazocine Phencyclidine	Dextromethorphan?

brain such as the lateral ventricles may cause tachycardia and hypertension. This and other evidence has led to the suggestion that the natural opioids may be involved in the pathogenesis of hypertension [77]. Which of these two opposing properties is manifest after administration of opioids in man depends upon the background activity of the autonomic nervous system. Depressor responses are more likely to occur in the presence of high sympathetic tone [8].

Gastrointestinal system

The antidiarrhoeal and constipative action of the opioids has both a central and a peripheral component. Mu receptor activation is probably responsible for the central action which is particularly important with more lipid-soluble opioids which produce constipation by this mechanism alone. Both kappa and mu receptors contribute to the reduction in intestinal propulsion in the periphery [83]. In addition, opioids have an antisecretory action on the intestinal mucosa, thus reducing fluid accumulation [46]—an action associated with delta receptor activation [48]. The introduction of peripherally acting antidiarrhoeal agents such as loperamide has been one of the few advances in the clinical use of opioids in recent years.

The enkephalins, dynorphins and beta-endorphin (co-localized with ACTH) are found in the gastrointestinal tract and, while much of the evidence concerning their activity is contradictory, it seems likely that they have a functional role, particularly with respect to intestinal secretion [40]. Although not strictly a gastrointestinal action, food intake also is affected by opioids. Agonists at most receptor types induce an increase in food intake, whilst naloxone suppresses feeding acutely but not chronically. Mu or mu$_1$ receptors are involved in some, but not all, aspects of increased feeding behaviour [49].

Endocrine system

It is clear that opioids are important modulators in the hypothalamus and thus can affect release of pituitary hormone. Prolactin release can be stimulated by both natural and unnatural opioids and there is evidence that beta-endorphin is responsible for stress-induced increases in prolactin concentration [27]. Opioids may stimulate release of growth hormone and reduce release of thyrotrophin, but the effects are inconsistent and probably do not reflect an important role in the physiological control of these hormones in man. An early property to be associated with kappa receptor activation was increased urination [42]. It has now been demonstrated that most opioids inhibit release of vasopressin [22] when the system is stimulated osmotically. However, they may also stimulate release in response to volume-mediated stimuli.

CONCLUSIONS

The large number of natural ligands to opioid receptors, some of which are represented in figure 1, and the complexity of their interactions with opioid receptors have slowed the progress of opioid research. This is in contrast with the more therapeutically successful area of adrenoceptor ligands, of which two occur naturally: noradrenaline and adrenaline. Opioid receptors come and go and there will be no real clarification of the exact number of different receptors until their structure is described. Whilst knowledge of some selective agonists and antagonists at individual receptors has resulted from manipulations of either opioid peptides or alkaloids (table I), their pharmacological profile awaits elucidation. Studies based on peptide compounds are fraught with problems of interpretation because of difficulties of penetration to their site of action. Even so, peptide drugs which have been shown to have an analgesic action have retained the tolerance and dependence liability of classical opioid drugs [73]. Indeed, although it has been shown that tolerance occurs to mu, delta and kappa receptor activation and that there is no cross tolerance, the mechanisms of tolerance and dependence production *in vivo* remain unknown [25].

A high proportion of the work attempting to link receptor to pharmacological action has revealed complex interactions between receptor types. The responses obtained depend not only upon activation of other opioid receptors, but also on the activation of other peptide and non-peptide neurotransmitter receptors. Thus the response observed may depend on the method used to measure it [82]. It is apparent that activation of different opioid receptors by a given drug occurs in stress and no-stress situations. The development of totally selective agonists may overcome this problem.

Of necessity, the majority of the experimentation aimed at the elucidation of opioid systems has been carried out in animals. However, the concentration and distribution of opioid receptors differs between the species. Human brains contain 29 % mu receptors, 34 % delta receptors and 37 % kappa receptors. In contrast, rat brain has 41 % mu receptors, 50 % delta receptors and only 9 % kappa receptors [50].

The net result of the difficulties described above is that, whilst many prototype opioid analgesics have looked promising in animal studies, they have failed to live up to their potential in man. Inevitably, this has led to a loss of confidence by the pharmaceutical industry in this area of research and the reduction of funding for opioid research in industrial laboratories and academic laboratories relying on industrial sponsorship. It remains the responsibility of the non-commercial grant-awarding bodies to ensure that opioid research eventually benefits mankind.

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ACCURACY OF PLACEMENT OF EXTRADURAL NEEDLES IN THE L3–4 INTERSPACE: COMPARISON OF TWO METHODS OF IDENTIFYING L4

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SUMMARY

The certainty with which the L3–4 vertebral interspace can be identified was investigated by studying 50 cadavers. These were allocated randomly to two groups, differing in the way in which the L4 spinous process was identified. Identification of L4 by physically constructing Tuffier's line on the subject led to an increase in the number of catheters sited at the correct level (P < 0.01).

KEY WORDS

Anaesthesia: extradural, spinal.

There is a wide variation in the vertebral level at which the spinal cord terminates: from T12 to the L3–4 intervertebral disc [1]. Although 51% of adult cords terminate at the L1–2 disc, 12% end at the L2–3 disc or below.

The height of block after induction of both intra- and extradural anaesthesia is related to the level at which the injection is made. One study has shown that intradural analgesia may reach as high as T1 with injection at the L2–3 space, but only as high as T6 with injection at L4–5 [2]. Similarly, for extradural analgesia, injection at L2–3 gave a maximum block height of T3, while injection at L5–S1 caused the block to extend only as high as T11 [3]. The authors of both these studies commented that the amount of haemodynamic instability was greater with injections made at a higher vertebral level.

Thus it is important to know at what level the needle is inserted for regional analgesia. However, it has been shown that intradural needles were not in the expected space on 50% of occasions, being sited one space too high or too low [4]. This study was designed to determine the accuracy of placement of extradural needles.

METHODS AND RESULTS

The study was performed in accordance with local Ethics Review policies. Following consent from the next of kin, 50 cadavers undergoing post-mortem examination were allocated randomly to one of two groups.

In group 1, subjects were placed in the left lateral position, their upper iliac crest palpated and the L4 spinous process identified by dropping an imaginary vertical line from the iliac crest to cross the midline at L4 or the L4–5 disc. An extradural catheter was inserted into the space above (the presumed L3–4 space) using a lateral approach.

In group 2, subjects were placed in the left lateral position and L4 was identified by stretching the extradural catheter between the two iliac crests to construct Tuffier's line [5]. The catheter was placed as before, at the presumed L3–4 level.

In both groups, a midline incision was made over the lumbar spine from the sacrum to the lower thoracic vertebrae. The erector spinae muscles were freed from the vertebrae and the catheter could be seen crossing the incision laterally to medially to enter the vertebral column at an interspace. That interspace was identified by counting upwards from the sacrum.

In all subjects physical characteristics were recorded: sex, age, height, weight and body mass index (table I).

Data were analysed using a two-sample *t* test for the physical data and a chi-square test with

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TABLE I. *Subject characteristics, actual level of placement of the catheters and significance (means* (SD) *or number)*

	Group 1 ($n = 27$)	Group 2 ($n = 23$)	P
Age (yr)	74.5 (9.4)	73.3 (13.2)	ns
Sex (M/F)	17/10	7/16	ns
Height (cm)	167 (9.6)	166 (9.3)	ns
Weight (kg)	69 (17.6)	61.6 (5.9)	ns
Body mass index	24.6 (5.5)	22 (4.6)	ns
No. catheters at:			
L2–3 (or above)	9 (33.3%)	1 (4.3%)	
L3–4	16 (59.3%)	18 (78.3)	0.01
L4–5	2 (7.4%)	4 (17.4%)	

Yates' correction for the catheter positions and sex, combining cells where necessary. A P value of 0.01 was taken as being significant.

In the freehand (group 1) method of identifying L4, 33% of catheters were placed too high, but in group 2 (constructing Tuffier's line), 80% of catheters were placed correctly and only 4% placed too high (table I).

COMMENT

In addition to the factors examined in this study, the level at which catheters are placed may be affected by bony abnormalities of the lower vertebrae which are common, particularly lumbarization of S1 and sacralization of L5. There was a case of partial fusion of L5 to S1 in group 1 in this study and the catheter in that cadaver was inserted too high.

It may be argued that performing regional analgesia at the L2–3 level rather than at L3–4 does not greatly increase either the amount of hypotension experienced or the amount of risk to which the spinal cord is exposed. It is important, however, that practitioners of regional analgesia realize that the spinal cord does not always terminate at the L1–2 disc, and that identification of a disc space may be inaccurate.

In one of the cases in group 1, a short man with narrow disc spaces, the needle was inserted at the L1–2 level. In these circumstances the resultant block height would have been noticeably higher than anticipated, and the spinal cord would have been exposed to considerably more risk of damage. Thus, while the added risk involved in placing the needle too high is small in most subjects, occasionally it may be considerable. It is noteworthy that this risk may be diminished by physically constructing Tuffier's line.

In conclusion, standard methods of identifying L4 are not particularly accurate, and are likely to lead to many spinal and extradural blocks being inserted at a level higher than expected.

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BACTERIAL MENINGITIS FOLLOWING SPINAL ANAESTHESIA FOR CAESAREAN SECTION

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SUMMARY

We report a case of meningitis caused by inadvertent introduction of bacteria following spinal anaesthesia for Caesarean section. The technique of performing the spinal anaesthesia is reviewed. Meningitis may occur, although very rarely, despite meticulous aseptic techniques. It is vital that meningitis should be considered in the differential diagnoses of post-spinal headache when patients present with headaches, pyrexia and meningism in the postoperative or postpartum period.

KEY WORDS

Anaesthetic techniques: spinal. Complications: meningitis.

CASE REPORT

A 33-yr-old woman, para I, was admitted at term in early labour. It was decided that she required urgent Caesarean section in view of genital herpes. She was apyrexial and urinalysis was normal. Her general health was good and a previous pregnancy had resulted in a normal vaginal delivery.

Spinal anaesthesia was performed with the patient in the left lateral position and there was no evidence of local skin infection. The skin was prepared with chlorhexidine in alcohol. An introducer was inserted at the L2–3 intervertebral space. Two attempts with a 29-gauge spinal needle encountered bony resistance. A third attempt at the L3–4 interspace was immediately successful and clear cerebral spinal fluid (CSF) was aspirated. Hyperbaric bupivacaine 2 ml was injected, producing a block up to T4 within 10 min. The Caesarean section proceeded uneventfully.

The patient remained well until approximately 16 h after operation, when she complained of a severe generalized headache of abrupt onset for which she received an i.m. injection of papaveretum 20 mg. Six hours later her headache returned, associated with nausea and marked photophobia. She was irritable and rapidly became drowsy. On examination, she was found to have a pyrexia of 39 °C, nuchal rigidity and a positive Kernig's sign. The differential diagnoses were meningitis, herpes encephalitis and post-spinal headache.

Lumbar puncture was performed; the CSF appeared turbid and the pressure was 18 cm H_2O. Analysis of CSF revealed a white cell count of 4000 mm^{-3} (100% polymorphs), protein 2 g $litre^{-1}$ (normal range 0.1–0.4 g $litre^{-1}$) and glucose 0.4 mmol $litre^{-1}$ (normal range 2.5–4.5 mmol $litre^{-1}$). No organism was seen on Gram staining and the culture remained sterile 1 week later. A diagnosis of "introduced" bacterial meningitis was made. To ensure that uncommon and highly resistant species of bacteria were covered, the patient was treated immediately with a broad range of i.v. antibiotics, including benzylpenicillin, cefotaxime, flucloxacillin and gentamicin. She made an uneventful and complete recovery.

DISCUSSION

Meningitis following lumbar puncture, spinal or extradural anaesthesia is extremely rare. The aetiology has been reviewed recently [1]. All the cases reported may be classified as bacterial, aseptic (chemical) or viral meningitis. Differentiation between bacterial and aseptic meningitis is difficult, but the latter is characterized usually by a normal CSF glucose concentration and negative culture. Pretreatment with antibiotics may lead to a negative Gram stain and culture, but this was not the case in this patient. Harter and Petersdorf reported that the Gram stain permitted

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identification of the causative organism in 80% or more of patients with untreated bacterial meningitis [2]. The CSF cultures have been reported as positive in only 70–85% of cases of bacterial meningitis [3].

Laboratory cultures are not designed to isolate the fastidious or unusual organisms which most probably accounted for this case of meningitis. Patients with negative CSF Gram stain and bacterial culture may be considered to have the "aseptic meningitis syndrome", but these do not exclude an aetiological role for bacteria [4]. The characteristic CSF profile [5] in this patient would be expected in a case of classical bacterial meningitis. This diagnosis was made after all the available CSF results were evaluated in conjunction with the clinical features.

Genital herpes simplex virus (HSV) infection afflicts 0.5–1.0% of pregnant women [6]. These parturients often require Caesarean section to minimize the risk of neonatal HSV infection, with its high morbidity and mortality rates. Infection may be primary or recurrent. The primary episode [7] is associated with viraemia and is characterized by fever, headache, malaise, myalgia, lymphadenopathy and other signs of meningeal irritation. HSV meningitis has been reported to occur in 8% of patients with primary infection [7]. In recurrent infections, systemic symptoms are infrequent and 25% are asymptomatic. There are two problems in the use of extradural or spinal anaesthesia in parturients with genital HSV infection: a risk of introducing virus into the central nervous system, and the medico–legal implications of disseminating herpes infection (which occurs exclusively with primary infection), despite the lack of causal relationship and the absence of documented case reports in recurrent episodes amongst otherwise healthy parturients. Extradural anaesthesia for Caesarean section has been used safely in a total of 153 patients with recurrent genital HSV infections, by three independent establishments [8–10]. These included 123 high risk patients whose recurrent infections were proven to be active. There were no reports of anaesthetic, septic or neurological complications related to the regional anaesthesia. However, there are no data or experiences, at present, on the safety of regional anaesthesia in patients who have primary HSV infections with systemic symptoms.

A thorough knowledge of aseptic techniques [11] is of paramount importance in performing spinal or extradural anaesthesia. Before the procedure, the trolley is normally wiped with 70% alcohol and allowed to dry. The dressing pack supplied by the hospital's Central Sterile Supply Department (CSSD) is opened and the inner pack placed on the trolley top. The inner wrap is opened by handling the corners only and forms the sterile field. Sterile disposable syringes, needles, spinal needle and its introducer and local anaesthetic ampoule are placed onto the sterile field. The hands are washed thoroughly with 4% chlorhexidine detergent or povidone-iodine. The hands of hospital staff who handle patients are one of the most important vehicles of cross-infection. It has been demonstrated that washing with soap and water eliminates 99% (10^2) of organisms from the hands. Antiseptic detergent removes approximately 10^2–10^3 and 70% alcohol 10^3–10^4 [12]. A sterile gown and gloves are then worn, as practised in the operating theatres.

A face mask is not worn, as it is of doubtful value in this context. Its principal role is to protect the patient against organisms dispersed from the upper respiratory tract of the attendant staff. The efficiency of various disposable masks has been investigated by several workers [13] and reviewed by Ransjo [14]. The theatre type masks, made of synthetic fibres such as polypropylene and polyester, have excellent biological filtration efficiency and protect the patient extremely well. The cheap paper masks provide very little protection and are potentially dangerous, as they create a false sense of security. The use of masks in operating theatres and wards has been questioned. Ritter and colleagues [15] reported no differences in the total number of airborne bacteria in the operating rooms during operations with and without masks, and Orr [16] concluded that there was no increase in the incidence of wound infection in general surgery, following the use of no masks in one operating theatre for 6 months. Earlier studies [17] revealed no evidence of transfer of *Staphylococcus aureus* from nurses' noses to wounds when masks were not worn for wound dressing on the wards. *S. aureus*, commonly present in the nose, is unlikely to be dispersed in the air in large quantity directly from a carrier by breathing and talking. It is more likely to be spread by handling the patient without first washing the hands, after touching the mask. A review of the literature [18] concluded that there was little risk if masks were not worn on the wards. Data based on prevalence surveys of 41 hospitals in the West Midlands revealed that the

TABLE I. *Properties of disinfectants (reproduced with permission from* [23]). *GPC = Gram-positive cocci; GNB = Gram-negative bacilli; TB =* Mycobacterium tuberculosis. ++ = *High*; + = *moderate*; − = *nil*

	Activity against			
Disinfectant	GPC	GNB	Spores	TB
70% Alcohol	++	++	−	+
Chlorhexidine	++	++	−	−
Iodophores	++	++	+(slow)	+

wound infection rate was not obviously influenced by wearing masks and protective clothing for dressing wounds [19, 20]. It is now recognized that the practice of wearing masks for ward procedures contributes little to patient or staff safety. There is, however, uncertainty on the use of masks for lumbar puncture on the wards. There is no evidence that the use of a mask contributes to preventing infection in this procedure [20]. However, some authorities [21] may still recommend their use.

A solution of 0.5% chlorhexidine in 70% alcohol is used for cleaning the lumbar region for 3–4 min and the disinfectant is allowed to dry. Any excess is wiped off the skin over the intended spinal puncture sites, after towelling the lumbar region with a sterile drape. Great care is taken at all times to ensure that the gloves and spinal needle are not contaminated with disinfectant.

"Disinfection" [22] implies the destruction of pathogenic organisms, but usually excluding bacterial spores. Ideally, all vegetative microbes such as *Staphylococcus* and viruses should be eliminated, but a reduction in the number of pathogens to a level that is unlikely to cause infection is usually acceptable. Alcohol, chlorhexidine and iodophores are all antiseptics that can be applied to skin without causing undue tissue damage. Their antimicrobial activities are shown in table I.

Alcohol is a rapidly acting (less than 30 s) disinfectant. It has the additional advantage that it leaves surfaces dry. The concentration of 70% is optimal *in vitro* for its action. The addition of non-volatile antiseptic (e.g. chlorhexidine) confers a residual antiseptic action on the skin, but does not significantly increase the efficiency of the alcohol. Chlorhexidine 0.5% in 70% alcohol is useful for preoperative preparation of the skin. In comparative studies, it has been found to be the most effective disinfectant, without causing skin reactions. It should be applied for 3–4 min, as repeated applications increase its efficiency. Some bacteria, notably *Pseudomonas aeruginosa*, may multiply in deteriorating chlorhexidine solutions. Therefore it is important to check the expiry date of the solution before use. Iodophores (e.g. povidone-iodine) are complexes of iodine and solubilizers with activity similar to that of iodine, but are non-irritant and do not stain skin. They kill most organisms within 10–60 s of contact and are also active against spores if left on the skin for more than 20 min.

After allowing the alcoholic chlorhexidine to achieve its maximal effects on the skin, in this patient, it required a total of three attempts at two vertebral interspaces to succeed in dural puncture. This obviously increased the risks of contamination and introduction of infection, despite working in a sterile field and handling the spinal needle using a "non-touch" technique. Sterile local anaesthetic was injected and the skin covered with an elastoplast to complete the spinal procedure.

The CSSD and respective manufacturers of disposable syringes, spinal needle and "Heavy Marcain" are entrusted with the sterility of their products. The last was contacted, and subsequent investigation revealed no evidence of contamination. However, standard aseptic procedures may not adequately decontaminate items or operating areas when the surface contains highly resistant or large numbers of organisms.

After a review of our practice of aseptic technique, it remains impossible to identify the exact source of the meningitis, but we conclude that there was no obvious flaw in procedure. This is an extremely rare case of bacterial meningitis caused by inadvertent introduction of bacteria despite a meticulous aseptic technique. Meningitis is a serious complication and its early diagnosis is vital. It may not be obvious clinically without lumbar puncture, in a patient who has had spinal anaesthesia and presents with pyrexia, headache and meningism in the postoperative period. Meningitis should always be considered as a possible differential diagnosis in patients with these symptoms and signs.

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BILATERAL CHYLOTHORAX

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SUMMARY

A 2.5-kg female developed bilateral chylothoraces 10 days after surgery for coarctation of the aorta. Initial conservative management consisted of intermittent positive pressure ventilation, drainage of chylous fluid and enteral feeding, but there was no diminution in loss of chyle. Ligation of the thoracic duct and pleurectomy were performed subsequently to reduce the large daily losses of chyle, amounting to nearly three times the child's circulating blood volume. Brawny oedema of the right upper quadrant of the body developed rapidly after the duct ligation and right pleurectomy. A further period of conservative treatment was required before the latter complication resolved. The literature relating to this iatrogenic complication and to fluid and nutritional losses in paediatric chylothorax is reviewed and discussed.

KEY WORDS

Complications: chylothorax Surgery: paediatric

Traumatic chylothorax in childhood is a recognized complication of cardiothoracic surgery, occurring in 0.2–1% of cases [1]. It may occur following venous cannulation of the subclavian and internal jugular veins [2–4]. It has been reported to appear many days after cardiothoracic surgery [5–8]. Bilateral chylothorax is rare, but it may occur after extensive dissection in the thoracic cavity, damage to both the thoracic and right lymphatic ducts during venous cannulation, or central venous obstruction arising from thrombosis [3] or venous cannulation [2].

The management of chylothorax is generally conservative and is based on enteral and parenteral feeding, continuous drainage of chyle and intermittent positive pressure ventilation (IPPV). Surgical intervention, commonly by low thoracic duct ligation, is advocated if conservative therapy fails to close the leak within a few weeks, or massive fluid and nutritional losses present dangers to the patient [9, 10]. The results following low thoracic duct ligation are good [9, 11].

CASE REPORT

A 2.5-kg female infant presented with cardiac failure at age 14 days, having been generally unwell and being dyspnoeic during feeds. Echocardiography demonstrated a large ventricular septal defect, atrial septal defect, severe coarctation of the aorta with proximal hypoplastic arch and bicuspid stenosed aortic valve. An earlier admission for malaise and breathlessness caused by cardiac failure was treated with digoxin and diuretics, with a good response.

Before surgery, initial treatment consisted of IPPV, diuretics and dobutamine. The echocardiographic findings were confirmed with cardiac catheterization. Extensive mobilization of the aorta, coarctectomy with side-to-side anastomosis and pulmonary artery banding, was carried out at age 20 days. Inotropic support via a double-lumen catheter in the right subclavian vein, IPPV and enteral feeding were required for the following 10 days, as the child remained in cardiac failure.

Percutaneous balloon aortic valvoplasty via the femoral artery was carried out successfully when the child was 1 month old and weighed 3 kg. During the subsequent 18 h she became acidotic and hypotensive, and developed a brawny swelling of the right side of the neck. Handling of the child led to bradycardia and other adverse haemodynamic changes. Serial chest radiographs showed developing consolidation in the right upper zone with fluid, initially in the right pleural cavity, and then in the left. Bilateral chest drains

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were inserted and 172 ml of serous fluid was drained. A milk test feed confirmed the presence of chyle in the fluid.

An enteral feed, rich in protein and medium chain triglycerides, was started. The right subclavian venous catheter was removed in case it was obstructing venous flow and contributing to the cause of the chylothorax. Despite supplementary parenteral feeding and adequate replacement of the measured protein and fluid loss, the infant lost 200 g in weight. Positive end-expiratory pressure (PEEP) (5–10 cm H_2O) was applied, with no apparent reduction in chyle flow.

Over the next 3 days, the chyle losses were greater from the left than the right chest. Total losses averaged 584 ml day^{-1}, with a maximum of 610 ml day^{-1} The lymph had a protein content of 29 g litre^{-1} and a white cell count of 0.9×10^9 cm^{-3} (95% lymphocytes).

Following a milk feed to define the leak, the right chest was opened and the thoracic duct was ligated supradiaphragmatically. Those sites where there was a visible leak of fluid at the apex of the thoracic cavity were cauterized and right pleurectomy was performed. Chest drainage decreased and enteral feeding was recommenced. The brawny oedema of the neck spread rapidly to the face, right arm and chest wall following pleurectomy. Body weight increased by about 100 g day^{-1}, from 2.8 kg to a peak of 3.9 kg.

The child's condition deteriorated again. She became acidotic, irritable and developed bradycardia with adverse haemodynamic changes and required inotropic support. Despite the presence of a drainage tube, at needle aspiration of the chest, a further 40 ml of serous fluid from the right chest and 70 ml from the left were drained. A second left thoracostomy tube was inserted. Moderate volumes of fluid continued to drain for the next 5 days. Over the following 10 days, her weight decreased gradually to 2.9 kg and there was associated resolution of the brawny oedema.

The child was discharged home, having spent a total of 86 days in hospital. She was well and had reached a weight of 3.5 kg.

DISCUSSION

The thoracic duct arises from the cisterna chyli at the level of the first lumbar vertebra. It enters the thorax beside the aorta and then ascends in the posterior mediastinum to the right of the midline. At the level of the 5th thoracic vertebra, it crosses to the left side and enters the venous system at the junction of the left subclavian vein and left internal jugular vein. The thoracic duct has tributaries from the lower intercostal spaces, the posterior mediastinal lymphatic glands, and the upper left intercostal spaces. The right lymphatic duct drains lymph from the right arm, right side of head and neck, right hemithorax and lung into the great veins on the right side. There is considerable anatomical variation, and cross connections may occur between pulmonary lymphatic channels and the internal mammary system [5, 10–13].

The thoracic duct is liable to injury during cardiothoracic surgery because of its proximity to the great vessels in the mediastinum. Damage to the duct has been reported after surgery for several congenital cardiovascular diseases [5, 8–10, 14]. The management of this problem has generally been conservative.

The principles of medical treatment are:

(a) Replacement of nutritional losses with a high protein diet rich in medium chain triglycerides [14–16], which are absorbed directly into the portal system. The normal daily protein intake is about 2.5 g/kg body weight. Occasionally, enteral feeding is not tolerated, so total parenteral nutrition should be instituted.

(b) Reduction of lymph flow by minimizing the fat content in the diet. IPPV with PEEP can depress lymph flow and may be required for prolonged periods [17, 18].

(c) Maintenance of full expansion of the lungs by continuous drainage of chyle using wide-bore pleural drains with suction. A close check on the volume and nutritional content of losses enables adequate enteral replacement. Sometimes, misleading information is obtained because the fibrinous chylous fluid obstructs the drainage tubes [7, 10]. Chyle may become loculated and require further insertion of pleural drainage tubes. At intervals, the drainage tubes may be clamped in an attempt to reduce the outflow of chyle by tamponade effect.

It is recommended that conservative treatment should be continued for a period of 1–6 weeks [1, 8, 16]. If this is unsuccessful in closing the fistula or if the volume of chyle lost is unacceptable, then surgical intervention should be undertaken. The surgical options consist of repair of the thoracic duct, supradiaphragmatic ligation of the thoracic duct, talc pleurodesis or pleurectomy.

In the patient described, bilateral chylothoraces presented 10 days after surgery and subclavian vein cannulation, and 18 h after balloon aortic valvoplasty. It was considered unlikely that the latter procedure was the cause of the problem. The balloon valvoplasty was performed percutaneously via the femoral artery. The site of dilatation was some distance from the thoracic duct. In 1987, Wren and his colleagues [19] from the U.K. interventional group of paediatric cardiologists reported a series of 13 cases of aortic valvoplasty in neonates and infants without evidence of chylothorax; this series now consists of 24 aortic valvoplasty procedures [personal communication]. In 1989, the same team reported a further 34 cases of balloon aortic valvoplasty in childhood, without chylothorax [20].

In our patient, chylothorax may have been caused by one or more factors: trauma to the thoracic duct at the initial operation, with chyle flowing across the midline through damaged pleura; obstruction to venous flow by the subclavian venous catheter causing chyle to leak out of the lymphatic system (removal of the catheter usually leads to resolution of the leak, which did not occur); trauma to the right lymphatic duct during venous cannulation, in addition to damage to the thoracic duct at operation.

Early surgical intervention was undertaken as the fluid and nutritional losses were in excess of previously reported volume losses of 4–200 ml kg^{-1} day^{-1} [5, 21]. The maximum fluid loss was 610 ml day^{-1} (218 ml kg^{-1} day^{-1}) and nearly three times the patient's circulating blood volume. It resulted in a substantial weight loss of 200 g, equivalent to 7 % of the child's body weight, over a period of 4 days.

The pitting oedema following ligation of the thoracic duct and pleurectomy spread rapidly along the distribution of the right lymphatic duct. There was no visible oedema over the rest of the body. It was caused, presumably, by cauterization of the opening of the right lymphatic duct into the venous system, resulting in an absence of an alternate pathway for lymph flow from the right upper quadrant. Alternative channels appear to have been formed within the following 3 weeks, as indicated by the resolution of the oedema.

Surgical pleurectomy or talc pleurodesis of the persistent left chylothorax would have stopped the loss of lymph into the chest, but it may have also exacerbated the widespread brawny oedema and added to problems with ventilation, nursing care and feeding.

In conclusion, bilateral chylothorax, although rare, does produce massive fluid and nutritional losses. Early surgical intervention reduces the volume of chyle lost, but in our patient produced severe upper quadrant oedema, which resolved within the following 3 weeks.

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PULMONARY OEDEMA FOLLOWING RELIEF OF UPPER AIRWAY OBSTRUCTION IN THE PIERRE–ROBIN SYNDROME: A CONSEQUENCE OF EARLY PALATAL REPAIR?

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SUMMARY

Pulmonary oedema occurred following relief of an acute upper airway obstruction in an infant with Pierre–Robin syndrome undergoing cleft palate repair. We anticipate an increased prevalence of this phenomenon in view of the present trend for early palatal repair, and would advocate the routine use of a nasopharyngeal airway after operation in infants with severe micrognathia.

KEY WORDS

Anaesthesia: paediatric Complications: airway obstruction, pulmonary oedema. Surgery: cleft palate.

There have been previous reports of pulmonary oedema occurring in association with acute upper airway obstruction in children [1, 2], although this is a rare complication. The increasing trend towards early cleft palate repair may lead to an increase in the incidence of this complication, particularly in infants with congenital abnormalities of the face and neck.

We present a case report of such a condition in an infant undergoing early cleft palate repair.

CASE REPORT

An 8-month-old, 8.5-kg girl with Pierre–Robin syndrome was admitted for repair of cleft palate. She had been delivered vaginally after prolonged labour. Difficulty with breathing at birth necessitated insertion of a nasopharyngeal airway which remained *in situ* for 2.5 weeks; following this she was nursed prone for 2.5 weeks in order to provide a satisfactory airway. Nasogastric tube feeding was necessary for the first 3 months of life because of difficulty with breathing during oral feeds. Subsequently, she suffered recurrent chest infections.

Although a history of feeding problems with possible bouts of aspiration pneumonia is suggestive of chronic airway obstruction, and pulmonary hypertension has been described in association with the latter in the Pierre–Robin syndrome [3], the patient was in good health on admission, with no abnormalities detectable on examination of the respiratory or cardiovascular systems. She displayed the characteristic micrognathia and low set ears of the Pierre–Robin syndrome.

Premedication comprised atropine 0.25 mg i.m. 45 min before operation. Anaesthesia was induced with cyclopropane in oxygen. A clear airway was maintained with continuous positive airway pressure by face mask and, after a trial of hand ventilation, suxamethonium 15 mg was given i.v. Laryngoscopy revealed a Grade III difficult intubation according to the classification proposed by Cormack and Lehane [4]; however a 4.0-mm orotracheal tube was passed without undue difficulty using a Mackintosh laryngoscope and gum elastic bougie. Anaesthesia was maintained with 70 % nitrous oxide and 0.5 % halothane in oxygen. Ventilation using a Penlon–Nuffield 200 ventilator with Newton valve was facilitated by a bolus dose

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of atracurium 3 mg followed by an infusion of 4–8 μg kg^{-1} min^{-1}. Monitoring included praecordial stethoscope, ECG, non-invasive arterial pressure and pulse oximetry. Neuromuscular block was monitored with a peripheral nerve stimulator.

During the procedure, 50 ml of 4% glucose/0.18% saline was infused. Blood loss was estimated as 15 ml. Surgical repair of the palate proceeded uneventfully and, after 1 h, residual neuromuscular block was antagonized with neostigmine 400 μg and atropine 200 μg.

The tracheal tube was removed when the child awoke, but she became acutely obstructed; intermittent positive pressure ventilation by mask was impossible and immediate tracheal reintubation was required. Transient cyanosis was observed; a small amount of frothy, blood-stained fluid was aspirated from the tracheal tube soon after its reinsertion. The trachea was extubated a few minutes later and a shortened Portex tracheal tube was inserted as a nasopharyngeal airway to which 5 cm of continuous positive airways pressure was applied. The tube was secured with a Tunstall connector and conventional fixation.

Continuous pulse oximetry revealed a saturation of 87% (with $F\mathrm{I}_{\mathrm{O}_2}$ 0.6) and this soon increased to more than 90% after the patient was transferred to the high dependency unit. A chest x-ray at this time showed bilateral lung shadowing consistent with pulmonary oedema. The nasopharyngeal airway was removed 4 h later and oxygen was provided via a nasal catheter at 1 litre min^{-1}. Oxygen saturation was maintained greater than 90%. A chest x-ray taken 6 h later showed almost complete resolution of the former shadowing. Oxygen therapy was discontinued the following morning and the child returned later to the general surgical ward. Her subsequent recovery was uneventful and she was discharged home on the 6th day after operation.

DISCUSSION

Acute pulmonary oedema is well recognized in association with episodes of acute upper airway obstruction, occurring during or after relief of obstruction [2, 4, 5]. Previous case reports have indicated no underlying medical disorder to account for the sudden onset of pulmonary oedema, which appears to be related only to relief of acute upper airway obstruction. There appears to be no fixed time interval between the relief of obstruction and the onset of oedema, or any relationship between the duration of obstruction and the appearance of oedema [6]. In children, early onset of oedema within a few minutes of relief of obstruction is more likely than in adults.

Characteristically, patients recover rapidly with prompt diagnosis and treatment. Primary treatment consists of the application of positive airways pressure and a high inspired oxygen concentration. Intermittent positive pressure ventilation, positive end-expiratory pressure, diuretics and steroids may be required.

The mechanism by which pulmonary oedema occurs in this setting is probably multifactorial. Several theories have been proposed [2, 5, 7, 8]; one plausible aetiology related obstructed respiration with massive transpleural pressure changes and alveolar–capillary membrane damage.

The recovery period after cleft palate repair may be complicated by a compromised upper airway, particularly in infants with congenital abnormalities such as Pierre–Robin syndrome; however, most cases may be managed satisfactorily by delaying tracheal extubation until the infant is fully awake.

The risk of this complication occurring is probably increasing with the trend towards corrective surgery at an earlier age than has formerly been the case. There is increasing evidence that speech is better if the palate is repaired at least before the age of 12 months, and many surgeons are now repairing the palate at 6 months or younger [9]. Even neonatal repair of the cleft lip has its advocates, although the majority of surgeons would favour repair at between 2 and 3 months of age. This subject has yet to be fully resolved; however, infants are presenting for early cleft palate repair and the postoperative management of the airway should be carefully considered.

Although the insertion of a tongue stitch before tracheal extubation has been practised routinely in some centres, this has now largely fallen into disrepute because of the pain and restlessness which it undoubtedly causes.

As infants are obligatory nose breathers, despite the theoretical risk of damage to the palatal repair, the careful insertion of a nasopharyngeal airway before extubation is probably the most reliable way of avoiding postoperative airway obstruction, and should be considered in all infants with severe micrognathia.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

EDINBURGH MEETING

November 9–10, 1990

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

CARDIORESPIRATORY EFFECTS OF SUFENTANIL

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Sufentanil is a thienyl analogue of fentanyl, with an analgesic potency up to 10 times that of fentanyl [1]. Its cardiovascular effects have been examined in patients undergoing major and cardiac surgery. However, we are not aware of any reports on the action of sufentanil on cardiovascular responses when used alone.

Thirty unpremedicated, ASA I and II, male and female patients gave informed consent to the study. Systolic, diastolic, mean arterial pressure, heart rate, ventilatory frequency, end-tidal carbon dioxide concentration and oxygen saturation measurements were made at 1-min intervals for 10 min using a Marquette series 7010 electronic monitor.

Patients were allocated randomly to three groups to receive a 10 ml i.v. bolus dose of sufentanil 0.05 $\mu g\ kg^{-1}$, 0.1 $\mu g\ kg^{-1}$ or saline. Baseline measurements were made before injection.

Data were analysed by repeated analysis of variance. No significant changes were observed.

We conclude that sufentanil in the doses used had no measurable effect on the cardiovascular and respiratory system.

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RESPIRATORY FUNCTION AND RIB CAGE CONTRIBUTION TO VENTILATION IN BODY POSITIONS COMMONLY USED DURING ANAESTHESIA

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Preoperative lung function tests are performed normally in an upright posture but during anaesthesia the patient is usually supine, occasionally lateral or prone, and rarely sitting. Many factors related to position influence the respiratory system and we have compared lung function in five body positions in awake volunteers.

Following Ethics Committee approval we measured forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and functional residual capacity (FRC) in 13 male subjects in five positions: sitting, supine, supine with arms raised, prone and left lateral. Closed circuit helium dilution was used to measure FRC. In addition we used respiratory inductive plethysmography [1] to measure the relative respiratory change in cross-sectional area of the rib cage (RC) and abdomen, and hence the contribution of the RC to ventilation expressed as %RC. All comparisons are with the supine position using two-way analysis of variance.

FEV_1 and FEV_1/FVC ratio did not differ significantly in any position. Apart from the well known increased %RC when sitting, there were no differences in %RC between the other positions (table I).

TABLE I. *Mean* (SD) *FVC, FRC and %RC in the five positions studied.* $^{**}P < 0.01$, $^{***}P < 0.001$ *compared with the supine position*

	FVC (litre, BTPS)	FRC (litre, BTPS)	%RC
Sitting	5.01 (0.9)***	2.91 (0.9)***	69.7 (11)***
Supine	4.71 (0.9)	2.10 (0.8)	32.3 (12)
Arms up	4.59 (1.0)	2.36 (0.8)**	33.0 (15)
Prone	4.63 (1.0)	2.45 (0.8)***	32.6 (11)
Lateral	4.87 (1.0)	2.44 (0.8)***	36.5 (17)

The 5% increase in FVC when sitting compared with supine is not relevant clinically and probably results from increased activity of respiratory accessory muscles. An increased FRC when sitting is well documented, but in the lateral position the FRC was also greater than when supine, probably resulting from cephalad shift of only the lower (left) diaphragm. When prone, the greater FRC compared to supine, may result from less cephalad shift of the relatively non-compliant costal part of the diaphragm. In both positions, a 350 ml change in FRC is more than half the usual decrease in FRC seen with anaesthesia, indicating that anaesthesia in these positions may result in less disturbance of gas exchange. Many studies of the effects of anaesthesia on ventilatory function are carried out in CT scanners where the subject's arms must be raised above the head [2]. This manoeuvre increases FRC by 250 ml indicating that these studies may underestimate the disturbance of gas exchange during normal supine anaesthesia.

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EFFECT OF INSPIRATORY AND EXPIRATORY RESISTANCES ON THE END-TIDAL POSITION IN MAN

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It is accepted generally that an increase in expiratory resistance causes an increase in end-tidal position (ETP) and by implication in functional residual capacity (FRC) [1]. It was demonstrated recently that FRC decreased when the nose was occluded overnight and it was suggested that the nose maintained FRC by acting as a resistance to expiration [2]. More recent work, however, has thrown doubt on this suggestion [3] so the relationship between resistance to ventilation and FRC (deduced from changes in ETP) has been re-examined.

Thirteen volunteers breathed via a spirometer circuit into which various resistances (scintered discs) of 0.06–0.28 cm H_2O litre^{-1} min^{-1} at flow rates of 25 litre min^{-1} could be inserted singly and in various combinations. In 12 subjects ETP increased in response to increased expiratory resistance, but in patient no. 13 ETP did not alter. When expiratory resistances that produced an increase in ETP of mean 255 (SD 28, BTPS) ml were applied intermittently (150 s in, 150 s out) the elevation in ETP in 10 subjects decreased to zero between the second and sixth (median third) application. In one subject ETP increased by 162 ml and remained increased throughout. In the 12th, ETP tended to decrease but by the sixth application was still above the preresistance value. When the resistance that had produced an increase in ETP on the expiratory side was applied to the inspiratory side in seven subjects, ETP showed a steady and progressive decline.

It is concluded that the increase in ETP produced by an increased expiratory viscous resistance is in most people only transient and if the nose maintains FRC it does so by mechanisms other than acting as a resistance to ventilation.

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CARBON DIOXIDE ELIMINATION FOLLOWING ACUTE LUNG INJURY INDUCED BY I.V. ETHCHLORVYNOL IN SWINE

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Ethchlorvynol (ECV) given i.v. produces damage to endothelium and permeability pulmonary oedema in swine. This results in an increase in deadspace ratio (V_D/V_T) and intrapulmonary shunt ($\dot{Q}sp/\dot{Q}t$) [1]. This mismatch of ventilation and perfusion impairs oxygen uptake and doubles $\dot{Q}sp/\dot{Q}t$. This study determined carbon dioxide elimination in this model of acute lung injury.

Institutional approval was obtained for the experiment. Six swine (40–45 kg) were anaesthetized with Innovar-Vet (fentanyl 0.4 mg and droperidol 20 mg ml^{-1}, 5 ml h^{-1}) and involuntary movement abolished with suxamethonium 5 mg kg^{-1} h^{-1}. Ventilation with nitrous oxide in oxygen at 15 ml kg^{-1} was given at a rate of 15 b.p.m. $F_{I_{O_2}}$ was raised from 0.21 when necessary to maintain Sa_{O_2} above 90%. Animal temperature was maintained at 38.0 ± 1.0 °C. Full monitoring of this model has been described [1]. The variables measured directly in this study included: (a) inspired/expired flow and concentration of oxygen and carbon dioxide ($\dot{V}_I$, $\dot{V}_E$, $F_{I_{O_2}}$, $F_{E_{O_2}}$, $F_{E_{CO_2}}$) by metabolic gas monitor; (b) Sa_{O_2} and $S\bar{v}_{O_2}$ and haemoglobin (Hb) by analyses of blood samples; (c) Pa_{O_2}, Pa_{CO_2}, pH by blood gas analyser. Using standard formulae or the Siggaard–Andersen nomogram the following variables were derived: (d) bicarbonate (HCO_3-), arterial and mixed venous carbon dioxide content (Ca_{CO_2} and $C\bar{v}_{CO_2}$) and carbon dioxide production ($\dot{V}CO_2$); (e) cardiac output ($\dot{Q}t$) was calculated using the Fick equation; (f) deadspace ratios (V_D/V_T) were derived from Pa_{CO_2} and $P\bar{E}_{CO_2}$ and $F_{I_{O_2}}$, $F_{A_{O_2}}$ and $F_{E_{O_2}}$. Where constants for swine were not available, human values were used. After obtaining stable baseline measures, ECV 55 mg kg^{-1} was infused into the pulmonary artery. Values were obtained at the end of infusion, 90 and 180 min after ECV. Results (mean (SD)) at these three times were compared with baseline by analysis of variance with repeated measures on time. Differences were significant at $P < 0.05$.

There was no difference in $\dot{V}_E$ over time. $F_{I_{O_2}}$ at the end of infusion (0.38 (0.17)), 90 min (0.31 (0.08)) and 180 min (0.34 (0.08)) were different from baseline (0.21 (0.05)). V_D/V_T rose from baseline (0.37 (0.05)) to (0.49 (0.08)), (0.48 (0.12)) and (0.48 (0.11)) (table II).

Effects we attributed to ECV were: a decrease in $\dot{Q}t$ from a negative inotropic effect with a decrease in $\dot{V}CO_2$ and an increase in V_D/V_T. We considered that these were the result of a decrease in alveolar perfusion and/or redistribution of pulmonary blood flow [2]. Although significantly different,

TABLE II. *Mean* (SD) *values of some ventilatory variables measured at baseline, the end of infusion, 90 and 180 min after ethchlorvynol.* *P < *0.05 compared with baseline*

	$C\bar{v}_{CO_2}$ (ml litre^{-1})	$\dot{Q}t$ (litre min^{-1})	Ca_{CO_2} (ml litre^{-1})	$\dot{V}CO_2$ (ml min^{-1})	HCO_3- (mmol litre^{-1})	pH
Baseline	606 (43)	5.8 (1.6)	569 (43)	210 (42)	26 (2)	7.45 (0.02)
End infusion	597 (49)	3.6 (0.7)*	545 (48)	183 (33)*	25 (2)	7.39 (0.05)*
90 min	653 (28)*	4.3 (1.9)*	605 (34)*	183 (26)*	27 (2)*	7.40 (0.04)*
180 min	625 (48)	4.8 (2.0)	581 (37)	193 (26)	26 (2)	7.40 (0.04)*

HCO_3- and pH remained in the physiological range [2]. We conclude that this model facilitates the study of oxygen transfer in acute lung injury without the additional factors of carbon dioxide retention and acid–base disturbance. This may in turn elucidate changes in early ARDS in humans.

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POSTOPERATIVE OXYGEN DESATURATION AND MYOCARDIAL ISCHAEMIA IN PATIENTS PRESENTING FOR VASCULAR SURGERY

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We have reported previously perioperative changes in arterial oxygen saturation (Sp_{O_2}) and silent ischaemia in patients undergoing vascular surgery [1]. One recent study examined the association of these two risk factors of cardiopulmonary dysfunction in the same patient group [2]

Eleven patients (nine male) undergoing elective aortic surgery were studied. ECG were recorded continuously before operation and for 48–72 h after operation using Oxford Medilog 6000 FD devices and a purpose-built computer analysis system. Sp_{O_2} was recorded continuously overnight before operation and for the first three nights after operation using an Ohmeda 3700 pulse oximeter and a portable computer. ECG data were analysed to determine the absolute and percentage time of ST segment depression $\geqslant$ 1 mm; Sp_{O_2} data were analysed as medians and ranges. Data comparisons were made using chi-square and Fisher's exact test.

Patients were studied for 18.2 (range 8.8–21.3) h before operation, and for 46.2 (24–69.5) h after operation. Time with and without ECG evidence of myocardial ischaemia and Sp_{O_2} data are shown in table III. Oxygen was given by face mask for the first 48 h.

Before operation ischaemia occurred in one of 11 patients compared with six of 11 after operation ($P < 0.05$). Duration of ischaemia was increased after operation ($P < 0.001$ for all comparisons). Silent ischaemia was greater on the third day after operation compared with the first two days ($P < 0.001$). On the third day, ischaemia occurred only in patients with an Sp_{O_2} value of less than 85% at some time during the study ($P < 0.001$).

We conclude that myocardial ischaemia increases in frequency and duration from before to after operation. The total ischaemic burden was greatest on the third day after operation and was associated with hypoxaemia after oxygen therapy was discontinued at 48 h.

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NOCTURNAL PATTERNS OF OXYGEN SATURATION FOLLOWING THORACOTOMY

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Postoperative hypoxaemia has pulmonary causes, such as atelectasis, and extra-pulmonary causes such as impaired ventilatory control as a result of the combined effects of opioid analgesics and sleep. Atelectasis is more likely after upper abdominal and thoracic surgery and will amplify the effects of impaired control on Sa_{O_2} in the postoperative period. Recent advances in computer processing of Sa_{O_2} data produce compressed arrays of Sa_{O_2} distribution [1] and serial centile plots. A previous study compared the effects on Sa_{O_2} distribution, hour-by-hour, of three postoperative analgesic regimens for lower abdominal surgery [1]. In the present study 20 patients undergoing thoracotomy for repair of hiatus hernia were monitored nightly from the night before operation until the fourth night after operation. Patients were allocated randomly to receive one of two analgesic regimens: paravertebral bupivacaine or saline infusions, with papaveretum i.m. as required in both groups. Oxygen was administered by a face mask for the first 24 h.

Hypoxaemia was defined as an Sa_{O_2} value below 94% for more than 12 min per hour. This corresponds to the 20th centile curve (i.e (20/100) × 60 min). On the night before operation all patients showed a small variability in Sa_{O_2} within each 1-h sampling interval. Eleven of 20 patients were not hypoxaemic, four were hypoxaemic for less than 3 h during the night and five were hypoxaemic for most of the night

TABLE III. *Perioperative oxygen saturation (Sp_{O_2}) values and time with and without myocardial ischaemia*

	Before operation ($n = 11$)	After operation Day 1 ($n = 11$)	After operation Day 2 ($n = 11$)	After operation Day 3 ($n = 8$)
No. with ischaemia	1	5	3	3
Duration of ischaemia in ischaemic group (% time)	2.7	15.0	13.7	54.4
Recorded time (h)	200	187.6	190.2	164.1
Mean overnight Sp_{O_2}				
Median	94.2	97	93.7	89.3
Upper range	97.3	99.5	98.1	93.2
Lower range	90.3	95.6	90.4	68.7

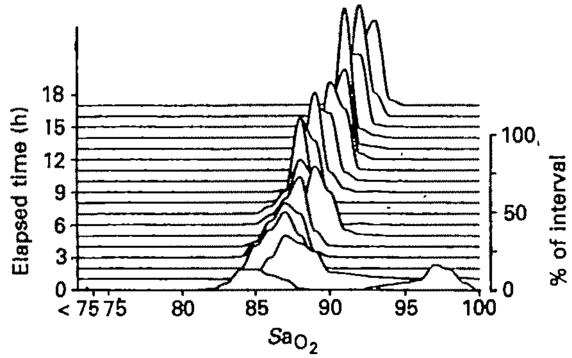

FIG. 1. Pattern of oxygen saturation (Sa_{O_2}) on the first night after operation.

During the first night after operation the Sa_{O_2} pattern fell into four groups: stable, not hypoxaemic (two of 20 patients); stable, hypoxaemic but improving (eight of 20 patients) (fig. 1); stable and constant hypoxaemia (five of 20 patients); and unstable, hypoxaemic and deteriorating (five of 20 patients). "Unstable" is a wide distribution pattern of Sa_{O_2} with considerable variability from hour to hour.

On the second night after operation, three of 20 patients were stable and not hypoxaemic, 12 were stable and hypoxaemic and five were unstable and hypoxaemic; four of these five were in the saline group having had more papaveretum than the bupivacaine group.

On the fourth night after operation, 16 patients were studied. All were stable but 11 were hypoxaemic. Of the five who were not hypoxaemic, two from the bupivacaine group had not reached their preoperative values.

All patients who were hypoxaemic before operation were hypoxaemic after operation. Postoperative hypoxaemia was predicted in only 50% of patients. Papaveretum led to a decrease in Sa_{O_2} in both groups. Regional anaesthesia did not provide any clear advantage in terms of Sa_{O_2} except that the requirement for papaveretum was reduced in the bupivacaine group.

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PREOXYGENATION TECHNIQUES IN THE ELDERLY

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Although many techniques of preoxygenation have been studied in adults [1], they have not been investigated thoroughly in the elderly, particularly with regard to ideal duration. In the present study we have assessed the duration of preoxygenation in the elderly during a modified rapid sequence induction by measurement of oxygen saturation.

One hundred ASA grade I or II patients, aged 65 yr or more were allocated randomly to five groups of 20 patients each. Patients with proven ischaemic heart disease, obstructive airways disease, obesity, anaemia or smoking within three months of surgery were excluded. Premedication was diazepam 5–10 mg 90 min before operation. ECG, arterial pressure and oxygen saturation were monitored throughout. Preoxygenation, which was carried out using a non-rebreathing circuit, consisted of four deep breaths of 100% oxygen over 30 s in group A using a fresh gas flow rate of 10 litre min^{-1}. Groups B, C, D and E were preoxygenated for 1, 2, 3 and 4 min, respectively. The anaesthetic sequence was preoxygenation, vecuronium 0.1 mg kg^{-1} and fentanyl 1 μg kg^{-1}, followed 30 s later by thiopentone 3–5 mg kg^{-1} Intubation was carried out 90 s after administration of vecuronium. Ventilation was not assisted and the tracheal tube was left open to room air until the patient's oxygen saturation reached the study end-point of 93%. Arterial blood samples were withdrawn for blood-gas analysis from the first five patients in each group, before and after preoxygenation, and at 95% and 93% saturation. Results were analysed using analysis of variance, Duncan's and Kruskal–Wallis tests.

The groups were comparable in terms of age, weight and oxygen saturation before and after preoxygenation (table IV). The mean times to reach 93% saturation were not significantly different between groups A and B or between groups C, D and E. However, mean times were significantly longer ($P < 0.05$) in groups C, D and E in comparison with groups A and B. Pa_{O_2}, where measured, was not significantly different between the groups either before preoxygenation or at 93% saturation. Pa_{O_2} values in each group before preoxygenation and at 93% saturation were not significantly different from each other.

Our results indicate that preoxygenation for 2 min or more produces a significant prolongation in the time taken to desaturate to 93% in the elderly in comparison with four deep breaths or preoxygenation for 1 min.

TABLE IV. *Mean* (SD) *age, weight and oxygen saturation before and after preoxygenation in the five groups*

	Group A	Group B	Group C	Group D	Group E
Age (yr)	78 (6)	77 (8)	77 (6)	77 (7)	77 (5)
Weight (kg)	60 (11)	63 (13)	62 (11)	56 (10)	65 (14)
Resting Pa_{O_2} (kPa)	11.3 (1.5)	10.7 (0.9)	11 5 (1.1)	11.6 (1.6)	10.7 (1.2)
Resting saturation (%, median)	97	97	96	97	96
Pa_{O_2} at 93% saturation (kPa)	10.3 (0.9)	10.4 (0.5)	11.2 (0.8)	11.3 (1.7)	11.1 (0.8)
Time to 93% saturation (min)	3.7 (1 6)	4.1 (1.2)	5.4 (1.7)	5.4 (1.4)	5.2 (1.7)

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ULTRASTRUCTURAL EVIDENCE FOR FREE RADICAL PRODUCTION DURING EXPERIMENTAL LUNG INJURY

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There is substantial evidence that the neutrophil is responsible for much of the tissue damage generated in many of the experimental models of acute lung injury. Phorbol myristate acetate (PMA) has been shown *in vitro* to trigger neutrophil activation, and *in vivo* causes pulmonary leucosequestration and acute haemorrhagic alveolitis. Associated with these changes is an increase in the permeability of the pulmonary capillary endothelium, and in keeping with the ability of PMA to stimulate the neutrophil's respiratory burst, there is evidence that oxygen-derived free radicals such as hydrogen peroxide mediate this lung injury. This study has examined the effect of PMA-induced neutrophil activation on the permeability of the other component of the alveolar capillary barrier, the alveolar epithelium. The structural correlates of any permeability changes have been examined using a cytochemical ultrastructural technique which identifies sites of peroxide activity.

Eleven New Zealand White rabbits were anaesthetized and the lungs ventilated with oxygen enriched air through a tracheostomy. An aerosol of ^{99m}Tc-DTPA was administered and the permeability of the alveolar epithelium assessed by measuring the clearance of radioactivity from the lungs before and after i.v. administration of PMA (Sigma) 60 µg kg^{-1}. At the end of the experiment the lungs were processed for transmission electron microscopy using a modification of a cytochemical technique in which cerium chloride reacts with peroxide ions to form electron dense deposits [1].

PMA induced a marked increase in the permeability of the alveolar epithelium. The maximum rate of clearance, as expressed by a clearance half-time, was mean 16.9 (95% confidence interval 13.1–20.7) min, compared with a mean control clearance half-time of 179 (121–236) min. This injury evolved to a maximum rate of clearance over a period of 30–90 min, and was followed by a period of apparent partial recovery. The ultrastructural studies have demonstrated some peroxide activity on the surface of the alveolar macrophage, but particularly between the alveolar epithelium and capillary endothelium in regions close to sequestered neutrophils. The epithelium in such regions was severely disrupted.

This study has demonstrated that the spectrum of PMA-induced lung injury includes damage to the alveolar epithelium as well as capillary endothelium. In addition, by localizing peroxide production to the sites of injury, this work supports the hypothesis that such injury is mediated by free radicals.

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DOES GLYCINE ANTAGONISM UNDERLIE THE EXCITATORY EFFECTS OF PROPOFOL AND METHOHEXITONE?

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We have investigated the pharmacological basis of CNS excitation that occurs in association with general anaesthesia. Propofol 125 mg kg^{-1} produced sustained clonic movements of all limbs in up to 85% of mice during the period of anaesthesia. Methohexitone 52 mg kg^{-1} produced intermittent non-rhythmic jerking in up to 50% of mice during anaesthesia. Two other anaesthetic drugs, ethanol 3.2 g kg^{-1} and pentobarbitone 32 mg kg^{-1}, produced anaesthesia without associated clonic movements. Doses of all anaesthetic drugs were equipotent in achieving an ED$_{90}$ value for loss of righting reflex at 5 min after intraperitoneal (i.p.) injection Surface EEG recordings showed paroxysmal discharges (high amplitude spikes and sharp waves) consistent with interictal manifestations of cortical seizures when mice were anaesthetized with methohexitone or propofol, but not when anaesthetized with ethanol or pentobarbitone.

The effects of very low doses of chemical convulsants on the behavioural and EEG manifestations of general anaesthetic drugs were assessed. Strychnine 0.3 mg kg^{-1}, a glycine antagonist without effects on the cerebral cortex, and bicuculline 1.1 mg kg^{-1}, a GABA$_A$ antagonist with effects on the cerebral cortex, were used at doses that were equipotent, that is, 0.5 log units less than the ED$_{10}$ value for clonic convulsions when given i.p. Strychnine potentiated significantly both the excitatory behaviour and the EEG paroxysmal discharges when given at the time of peak effect of methohexitone or propofol, but not when given with ethanol or pentobarbitone. Bicuculline did not affect either behaviour or EEG with any of the anaesthetic drugs.

Our data suggest that some anaesthetic drugs (methohexitone and propofol) produce CNS excitation while others (pentobarbitone and ethanol) do not. We propose that the pharmacological basis of the CNS excitation may be glycine antagonism occurring in subcortical structures. The fact that methohexitone and propofol are also anticonvulsant (against pentylenetetrazol and bicuculline, but not strychnine) suggest that some anaesthetic drugs may be simultaneously anticonvulsant and proconvulsant via different mechanisms. The identification of the pharmacological basis of excitation caused by anaesthetic drugs should allow this undesirable side effect to be screened out in future drug development.

SEQUENTIAL MEASUREMENT OF SOMATOSENSORY EVOKED POTENTIALS DURING ISOFLURANE ANAESTHESIA IN CHILDREN

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Determination of MAC requires a period of 15 min between reaching a stable end-tidal concentration of the volatile agent and application of the surgical stimulus [1], allowing equilibration between alveolar gas, arterial blood and brain. To date no objective neurophysiological studies have demonstrated that this equilibration occurs. In adults, changes in the median nerve somatosensory evoked potentials (MnSSEP) occur with increasing concentration of inhalation agent. The time from reaching the required end-tidal concentration and generating MnSSEP varies between studies from 10 to 15 min [2]. We have developed a technique based on the measurement of sequential MnSSEP in an attempt to determine this equilibration point.

Eight children (aged 10 months to 6 yr) were studied. The anaesthetic technique is described elsewhere [3]. MnSSEP were generated by applying a square wave DC voltage for 0.2 µs every 270 ms to the right median nerve, and recorded via silver scalp electrodes placed at P3 (10–20 system) with reference to Fz and the ipsilateral ear. Amplitude sensitivity was set at 100 µV with a band pass of 5 Hz to 3 KHz. A total of 256 repetitions were averaged with a sweep duration of 75 ms and MnSSEP obtained every 90–180 s allowing for electrical interference. Following control measurements in the absence of isoflurane the end-tidal concentration was increased stepwise (0.25, 0.5 and 0.75 MAC) and maintained for 15 min. End-tidal carbon dioxide, nasopharyngeal temperature and arterial pressure were measured throughout. The time at which the N20 latency reached stability was determined.

The time differences from achieving a stable end-tidal concentration of isoflurane and reaching N20 latency stability are shown in table V.

TABLE V. *Mean* (SD) *times to N20 latency stability after achieving desired isoflurane MAC*

	0.25 MAC	0.5 MAC	0.75 MAC
Time (min:s)	6:48	5:21	7:44
	(0:57)	(1:08)	(3:00)

In conclusion, we have demonstrated in children that the time to reach MnSSEP N20 latency electrical stability once a desired end-tidal concentration of isoflurane has been reached is less than 15 min.

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EFFECT OF ISOFLURANE ON THE N20 COMPONENT OF THE MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS IN CHILDREN

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The changes that occur with inhalation anaesthetic agents on the early cortical median nerve somatosensory evoked potentials (MnSSEP) have been described in adults [1]. Progressive reduction in amplitude and increase in latency of the N20 component of the MnSSEP occurs with increasing concentration of these agents. As yet no similar work has been performed in children. Evoked potentials are used in children to determine the integrity of the neural pathways during neurosurgical and orthopaedic procedures. Furthermore, MnSSEP may assist in determining "depth of anaesthesia". We have investigated these effects on the MnSSEP during isoflurane and nitrous oxide in oxygen anaesthesia.

Eight children (aged 10 months to 6 yr) undergoing surgical repair of hypospadias were studied. The anaesthetic technique was standardized: oral premedication was with trimeprazine 4 mg kg^{-1} and atropine 0.04 mg kg^{-1}. Anaesthesia was induced with halothane and nitrous oxide in oxygen. The trachea was intubated and the lungs ventilated with 70% nitrous oxide in oxygen following i.v. atracurium 0.5 mg kg^{-1}. Caudal extradural anaesthesia was achieved with 0.25% bupivacaine 0.5 ml kg^{-1}. After the halothane had cleared, control MnSSEP were obtained and isoflurane administered at 0.25, 0.5 and 0.75 MAC; the end-tidal concentration was held constant for 15 min. MnSSEP were analysed every 90–180 s during this period. Heart rate, ECG, arterial pressure, Sa_{O_2}, nasopharyngeal temperature, end-tidal carbon dioxide (5%), FI_{N_2O}, oxygen and end-tidal isoflurane were measured throughout. Raw EEG was recorded continuously. Analysis of N20 latencies, central conduction time and the N20–P22 amplitude was obtained in each patient compared with its control (ANOVA).

There were statistically significant increases in N20 latencies ($P < 0.05$) with progressively increasing end-tidal isoflurane concentrations compared with controls. Reduction in N20–P22 amplitudes were not statistically significant with these isoflurane concentrations ($P < 0.05$) (table VI).

TABLE VI. *Effect of isoflurane in 70% nitrous oxide on mean* (SD) *latencies and amplitudes of MnSSEP. CCT = central conduction time*

	N20 latency (ms)	CCT (ms)	N20–P22 amplitude (µV)
70% nitrous oxide	15.2	7.8	3.4
in oxygen	(1.2)	(1.5)	(2.0)
Isoflurane			
0.25 MAC	16.5	9.0	2.6
	(1.6)	(1.8)	(1.5)
0.5 MAC	17.7	10.2	2.1
	(1.4)	(1.6)	(1.1)
0.75 MAC	18.5	11.3	1.5
	(1.7)	(1.9)	(0.8)

Our results show an increase in the N20 latencies and a decrease in N20–P22 amplitude with increasing end-tidal isoflurane concentration, and are similar to the findings in adults [1].

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CHANGES IN AMPLITUDE AND LATENCY OF AN EVENT-RELATED POTENTIAL WITH DEPRESSION OF CONSCIOUSNESS BY NITROUS OXIDE

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One of the most extensively evaluated methods of assessing depth of anaesthesia is the measurement of change in latency and amplitude of the early cortical components of the auditory evoked potential [1]. Although these components show dose-related changes with anaesthesia, the short latency may mean that they mark the arrival of an input at the auditory cortex before any conscious processing of that input has occurred. The P300 is a much later, event-related potential which occurs when a rare stimulus replaces a regular stimulus in an unpredicable manner and its occurrence suggests that the difference between the rare and the regular stimulus has been registered, that is, that some processing has taken place. The P300 has been shown to change with low inspired nitrous oxide concentration [2] but it has not been studied with the higher concentrations used in routine anaesthetic practice. We have looked therefore at changes in the P300 in volunteers breathing nitrous oxide mixtures ranging from 30–80%.

Six subjects wore headphones and listened to clicks occurring at a rate of 1 Hz. Approximately 1 in 10 of these clicks were replaced in a pseudo-randomized manner by a tone and the subject was instructed to press a hand-held button as quickly as possible on hearing the tone. EEG was recorded from the vertex and referenced to linked ear lobes. The filtered and amplified EEG was fed to an averager which was triggered by the click preceeding the tone and sampled at 1 KHz for 3 s. Sixteen such sweeps were averaged to form each record. Records were obtained whilst the subjects breathed air and then whilst breathing different concentrations of nitrous oxide. End-tidal nitrous oxide, carbon dioxide and oxygen were monitored with a mass spectrometer.

As end-tidal nitrous oxide concentration increased, all subjects showed a decrease in P300 amplitude and an increase in P300 latency and in minimum reaction time. In four of the volunteers, a state was achieved at high nitrous oxide concentration in which the subject would no longer push the button in response to the tone but a P300 was discernible. Thus the P300 represented some persistence of central processing in the absence of a motor response to the tone. These results suggest that the P300 merits further investigation as a tool for detecting awareness under anaesthesia.

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FLOW RESISTANCE OF THE LARYNGEAL MASK IN AWAKE SUBJECTS

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The laryngeal mask airway [1] may be used in the spontaneously breathing patient and it has been advocated as an alternative to tracheal intubation.

We have measured airway resistance in a group of awake volunteers under local anaesthesia, before insertion of the laryngeal mask, with the mask in position, and after its removal, by means of the body plethysmograph [2]. Fifty-two sets of measurements were made in 12 subjects and the results were analysed using two-way analysis of variance.

Mean (SD) airway resistance before insertion of the laryngeal mask was 1.1 (0.7) cm H_2O litre^{-1} s^{-1}, with the mask in place 2.5 (0.7) cm H_2O litre^{-1} s^{-1} and after its removal 1.1 (0.4) cm H_2O litre^{-1} s^{-1}. There was no significant difference in the three measurements between subjects ($P < 0.26$) but a significant difference was observed within subjects ($P < 0.0001$). Further analysis with Fisher's protected least significant difference showed a significant difference ($P < 0.05$) between measurements with and without the mask *in situ* but none before and after its insertion. The mean airways resistance with the mask in place was similar to that found during tracheal intubation [3].

We conclude that the laryngeal mask airway offers significant resistance to breathing and that its magnitude approximates to that of a tracheal tube.

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A SERVO-CONTROLLED ANAESTHETIC MACHINE

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The machine in figure 2 comprises a totally closed anaesthetic system with a soda lime canister and a ventilator with rising bellows (Airshields Ventimeter). Anaesthetic agent, oxygen and nitrous oxide are added automatically to maintain preset values. The amounts added are measured continuously and represent the usage by the patient. A continuous display of the values and rate of usage are shown on a monitor and data are stored on disk.

The control system consists of a computer (Rockwell AIM 65) with additional circuit cards which receives input from an anaesthetic analyser (LAMTEC), fuel cell oxygen sensors

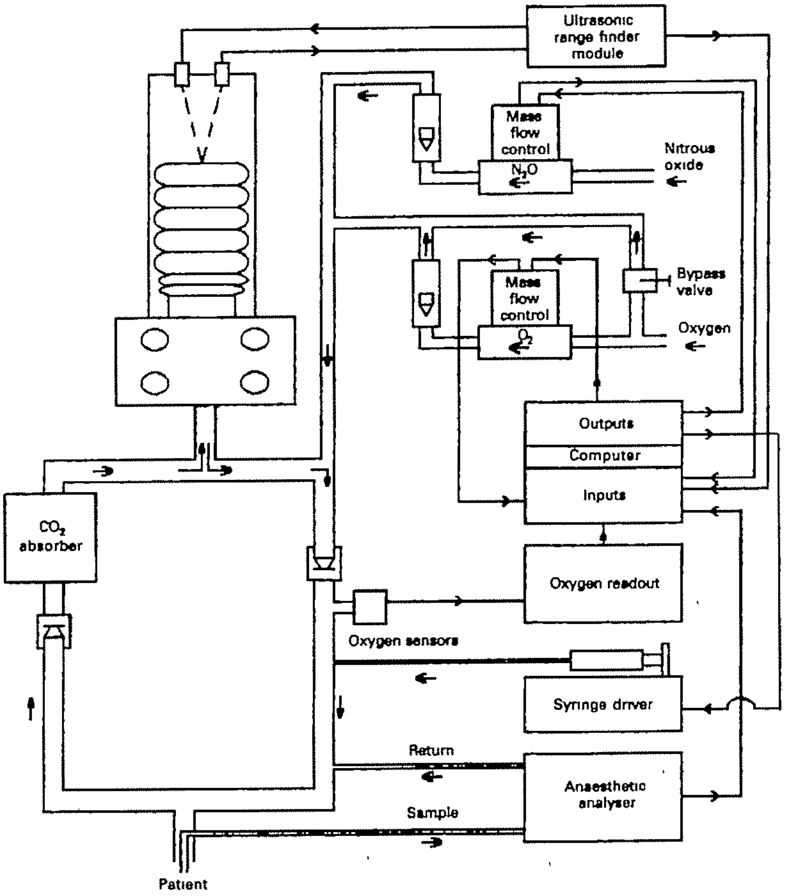

FIG. 2. Anaesthetic system.

(Teledyne T5) and an ultrasonic range finder (MASSA E-201) which measures the position of the ventilator bellows and hence changes in the volume of the circuit. Output signals are produced to control the injection of liquid anaesthetic by a syringe driver (VIAL SE 300) and to control the addition of oxygen and nitrous oxide using two mass flow controllers (MKS 1259B) which also measure oxygen and nitrous oxide flows.

Proportional and integral control is used. The control equations are of the form below and are recalculated once per breath.

$$\text{Output} = k_p(\text{error}) + \Sigma[k_i(\text{error})]$$

k_p and k_i are the proportional and integral constants, respectively.

Initially the output is controlled by the proportional component. The integral component of the drive builds up more slowly but maintains the output as the error signal reduces to zero.

$$\text{Anaesthetic flow (ml h}^{-1}) = 26{*}(\%\text{error}) + \Sigma(9.6{*}\%\text{error})$$

$$\text{Oxygen flow (ml min}^{-1}) = 18{*}(\text{O}_2\ \%\text{error}) + \Sigma(3.6{*}\text{O}_2\ \%\text{error})$$

$$\text{Nitrous oxide flow (ml min}^{-1}) = 2.4{*}(\text{volume error(ml)}) + \Sigma(0.24{*}\text{volume error(ml)})$$

The integral constants are adjusted for ventilation rate. The values above refer to breath intervals of 10 s.

The machine has been used clinically with both controlled and spontaneous ventilation.

FLUIDIC BISTABLE AMPLIFIER AS VAPOUR CONCENTRATION SENSOR

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A fluidic bistable amplifier oscillates within a simple flueric circuit [1] at a constant rate when supplied with gas at constant flow rate, pressure, density and viscosity, provided that these factors are within the normal working limits for the device. The addition of anaesthetic vapours to the supply gas stream, at concentrations within the normal clinical range, results in consistent changes in oscillation frequency of the fluidic device.

This effect was studied using nitrous oxide, enflurane, halothane and isoflurane. Oscillation frequency in a fluidic bistable device varied linearly in response to changes in anaesthetic agent concentration. Since the fluidic circuit was supplied with a gas mixture at constant pressure and flow, it seems that changes in oscillation frequency were caused by changes in viscosity and/or density of the supply gas.

It is clear that a simple fluidic device could be used within an anaesthetic circuit as a sensor for anaesthetic agent concentration. It is also evident that the underlying phenomena are not agent-specific, so it is unlikely that this type of sensor could be used as a means of identifying anaesthetic agents.

It remains possible, however, that a fluidic sensor could be used as a means of calibrating or checking vaporizers during clinical use, potentially without moving parts or electronics, or within a feedback loop system controlling anaesthetic vapour concentration.

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RELATIONSHIP OF BODY WEIGHT TO VOLUME OF DISTRIBUTION OF ATRACURIUM AND MAXIMUM TWITCH DEPRESSION

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It is usual to administer non-depolarizing neuromuscular blocking drugs in a dose related to body weight. It is not clear that this is warranted as, for example, with pancuronium the volume of distribution is not correlated with body weight [1]. An attempt has been made therefore to evaluate atracurium in this respect.

Thirty-eight healthy patients (aged 15–65 yr, weight 45–96.5 kg) undergoing minor surgery requiring neuromuscular block were studied in three groups. Anaesthesia was induced with fentanyl 50–200 μg and thiopentone 250–500 mg and maintained with 66% nitrous oxide in oxygen. In 14 patients anaesthesia was supplemented with isoflurane (0.9% end-tidal), in 14 with halothane (0.5% end-tidal) and in 10 with midazolam 3–10 mg. The EMG response of the adductor pollicis to train-of-four stimuli was recorded every 12.5 s throughout anaesthesia using a Medelec MS6. After control values had been taken, atracurium 0.25 mg kg^{-1} was administered by constant rate infusion over 10 min; blood samples were taken for assay of plasma atracurium concentration as described previously [2, 3].

Central and steady state volumes of distribution of atracurium were calculated and related to body weight as was the logit of the maximum depression of the first response of the train-of-four, A′/A.

When expressed as ml kg^{-1}, both central and steady state volumes of distribution had a strong negative correlation with body weight ($r = -0.621$ and $r = -0.732$, respectively). The absolute volumes (ml) did not correlate significantly, however ($r = 0.087$ and $r = 0.137$, respectively). The logit of maximum block differed between the three groups. Multivariate analysis showed that after the anaesthetic technique had been taken into account, the logit maximum block was correlated significantly with body weight ($F = 4.57$; 1, 34 d.f.; $P < 0.05$).

We conclude that the volume of distribution of atracurium is not directly proportional to body weight and administration of atracurium on a mg kg^{-1} basis leads to a greater effect in heavier patients.

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PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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The requirement for atracurium is reduced by approximately 50% by hypothermic cardiopulmonary bypass (CPB) [1]. Hypothermia reduces the rate of breakdown of atracurium [2] and it also reduces muscle contractility [3]. Plasma atracurium concentrations during CPB have not been reported previously.

Ten patients undergoing cardiac surgery with CPB were studied. Patients were premedicated with fentanyl 200 μg and droperidol 10 mg i.m. Anaesthesia was induced with midazolam 30–60 μg kg^{-1} and fentanyl 3–9 μg kg^{-1} and maintained with 0.5–1.0% trichloroethylene in nitrous oxide and oxygen. Nitrous oxide was discontinued before CPB. Neuromuscular monitoring (Datex Relaxograph) was commenced after induction but before a bolus of atracurium 0.6 mg kg^{-1}. When the first response ratio (T1/T0) had recovered by 5% a continuous infusion of atracurium at a rate of 7 μg kg^{-1} min^{-1} was commenced. The rate was adjusted to maintain 95% depression of T1. Nasopharyngeal and thenar skin temperatures were monitored continuously. The CPB circuit was primed with Ringer's lactate 1000 ml, Haemaccel 1000 ml, 10% mannitol 300 mg kg^{-1}, heparin 50 mg, fentanyl 500 μg and magnesium 0 1 mmol kg^{-1}.

Neuromuscular block was maintained at 96–99%. Onset of CPB was not associated with a significant change in plasma atracurium concentration. Twenty minutes after the onset of CPB (mean nasopharyngeal temperature 31.3 °C) the infusion requirement had fallen by 40% and at the minimum temperature recorded (mean 26.5 °C) atracurium requirement was 1.2 μg kg^{-1} min^{-1}, a decrease of 80% ($P < 0.001$). There was no significant change in plasma atracurium concentration or the degree of neuromuscular block.

The relationship between plasma atracurium concentration and neuromuscular block does not appear to change during CPB at the temperatures encountered in this study. The change in atracurium requirement during CPB may be due to a decrease in the rate of breakdown.

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INTRAOPERATIVE ASSESSMENT OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCK USING DOUBLE BURST STIMULATION

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Double burst stimulation (DBS) is a more reliable clinical method for the detection of residual paralysis than train-of-four (TOF) [1]. In this study we have assessed the mechanical response to DBS at levels of muscle relaxation suitable for intraoperative use.

Thirty-five fit adult patients were anaesthetized in a standardized manner including the administration of bolus atracurium. In the first group of 16 patients the ulnar nerve at the wrist was stimulated supramaximally with TOF stimuli followed 20 s later by DBS (pattern 3,3) [1] with the cycle repeated every 2 min. Isometric adductor pollicis muscle contraction was measured by a Grass FT-10 force displacement transducer, amplifier and chart recorder. Every third DBS contraction only was assessed manually by one of three blinded observers. The ratio of the first TOF twitch (T1) to control (C) was calculated and compared with the tactile evaluation of DBS twitch; the latter was scored as no response, single twitch or two twitches. The ratio of the measured height of the first DBS twitch (D1) to T1 was also calculated. A second group of 19 patients were stimulated with the same DBS pattern every minute until D1 became palpable. The post-tetanic count (PTC) was measured 20 s later.

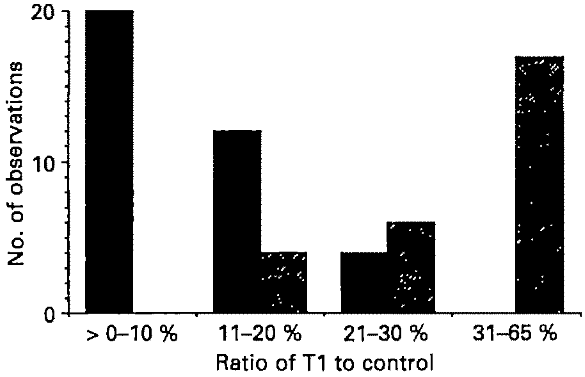

FIG. 3. Ratio of the first TOF (T1) to control compared with the tactile evaluation of double burst stimulation twitch. ■ = Single twitch; ■ = double twitch.

In the first group of patients the return of D1 always preceded T1 and was greater in amplitude by a mean factor of 1.9 (SEM 0.03) between a T1/C of 2 % and 65 %. When T1/C was between 0 and 10 %, a single twitch (D1) only was palpable; when T1/C was ≥ 30 %, both twitches were always palpable (fig. 3). Palpation of a single twitch suggests a 0.97 (35/36) chance of T1/C being < 25 % (based on 36 observations). In the second group of patients the return of the first D1 response corresponded with a median PTC of 7 (range 3–11).

The results suggest that DBS is a more sensitive indicator than TOF of return of neuromuscular function and may be appropriate for clinical use throughout the range of neuromuscular block.

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SEQUENTIAL AND SIMULTANEOUS ADMINISTRATION OF SUXAMETHONIUM AND ATRACURIUM

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Published work suggests that the effects of atracurium are potentiated by suxamethonium [1]. The first part of this study investigated the effects of suxamethonium for tracheal intubation on the pattern of subsequent atracurium block when the relaxants were given in a sequence comparable with usual clinical practice. The second part of the study examined the effects of simultaneous administration of suxamethonium and atracurium and evaluated the suitability of this technique to the clinical situation when there is a requirement for rapid tracheal intubation and an intermediate duration of action.

EMG (Relaxograph, Datex) from the adductor pollicis of

TABLE VII. *Extent, duration and recovery from atracurium block following administration of atracurium alone (group 1), atracurium followed by suxamethonium (group 2) and atracurium and suxamethonium in rapid succession. Values are mean (range)*

	Group 1	Group 2	Group 3
Maximum block			
Extent (%)	86.8 (80–100)	98.0 (80–100)	97.0 (93–100)
Latency (min)	5.68 (5.0–7.3)	1.3 (0.9–2.8)	1.2 (1.0–1.8)
25 % recovery (min)	19.9 (11.5–28.3)	21.8 (15.2–43.3)	22.1 (10.6–26.7)
Recovery index (min)	9.6 (6.0–13.0)	14.6 (7.0–33.1)	11.0 (7.3–16.6)
Intubation score	2.5 (1–3)	2.9 (2–3)	2.8 (2–3)

30 adult patients (ASA I or II) anaesthetized with thiopentone, fentanyl, enflurane and nitrous oxide in oxygen were analysed. Group 1 ($n = 10$) received atracurium 0.23 mg kg^{-1} as the sole relaxant. Group 2 ($n = 10$) received suxamethonium 1 mg kg^{-1} followed by atracurium 0.23 mg kg^{-1} when the EMG had recovered to 20% of the control value, a sequence intended to be representative of common clinical practice. Group 3 ($n = 10$) received suxamethonium 1 mg kg^{-1} and atracurium 0.23 mg kg^{-1} in rapid succession separated by physiological saline 5 ml. Conditions for tracheal intubation were scored [2] at 60 s in groups 2 and 3, and at 3 min in group 1. The patterns of block were analysed and the recovery index was obtained by permitting spontaneous recovery of the EMG to 75% of control in all patients.

Plasma cholinesterase was normal in all patients. Conditions for tracheal intubation were satisfactory in all groups. Suxamethonium for tracheal intubation (group 2) neither potentiated the subsequent atracurium block nor increased the duration (table VII). When suxamethonium and atracurium were given in rapid succession (group 3) the duration of suxamethonium block was reduced but the rate of recovery from the atracurium component was not significantly different from groups 1 and 2 (table VII).

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I.V. FLUIDS AND MINOR GYNAECOLOGICAL SURGERY: EFFECT ON RECOVERY FROM ANAESTHESIA

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I.v. fluid administration has been shown to decrease the incidence of postoperative morbidity after minor surgery under general anaesthesia [1, 2]. Assessment was by questionnaire, 6 h or longer after the procedure. I.v. fluids may also affect recovery from anaesthesia. We used two tests of psychomotor function to obtain an objective measure of recovery after general anaesthesia in order to compare a group who received i.v. fluids with a control group.

Thirty healthy unpremedicated women undergoing therapeutic abortion were studied. Before anaesthesia, subjects performed a letter cancellation test (B, D, E deletion), and a four-choice computer-controlled visual reaction and motor time test. Plasma and urine osmolality, and blood glucose were measured. Subjects were then allocated randomly to two equal groups. Group 1 received no fluids and group 2 received 4% dextrose 20 ml kg^{-1} and 0.18% saline. Anaesthesia was induced with fentanyl, propofol and nitrous oxide in oxygen. The tests were repeated 45 min after the end of anaesthesia. All testing was carried out by an observer unaware of group allocation. Statistical analysis was performed using analysis of variance, Student Newman–Keuls test, chi-square and Bonferroni t tests (paired within groups and unpaired between). $P < 0.05$ was considered significant.

One patient in group 2 was excluded for non-compliance. Last oral intake before anaesthesia was mean (SEM) 10 (0.75) h for group 1 and 10.4 (0.98) h for group 2. There were significant within-group differences in motor and reaction times in group 1 but not in group 2 before and after operation (table VIII). A study of approximately 500 patients is needed to determine the significance of the between-group differences.

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TABLE VIII. *Mean (SEM) plasma and urine osmolality, blood glucose and psychomotor function of the two groups. % > 600 ms, 400 ms = % of individual results taking longer than stated time.* *$P < 0.05$ *compared with values before operation*; †$P < 0.05$ *compared with other groups*

	Before operation		After operation	
	Group 1	Group 2	Group 1	Group 2
Blood osmolality (mosmol $litre^{-1}$)	274 (2.6)	277 (5.9)	272 (1.7)	266 (2.2)
Urine osmolality (mosmol $litre^{-1}$)	769 (66.1)	801 (45.3)	817 (64.5)	475† (97.3)
Blood glucose (mmol $litre^{-1}$)	4.1 (0.2)	4.2 (0.1)	4.4 (0.1)	5.3† (0.6)
Motor time (ms)	209.4 (11.9)	195.3 (11.3)	234.5* (13.9)	210.8 (17.7)
% > 400 ms	2.17	2.05	4.83*	3.92*
Reaction time (ms)	333.6 (14.9)	350.1 (17.3)	379.0* (20.5)	390.7 (31.6)
% > 600 ms	1.38	2.97	2.48*	5.93*
Deletion score	95.4 (3.8)	102.1 (1.6)	95.1 (2.8)	101.7 (0.9)

RECOVERY AFTER DENTAL SURGERY UNDER ANAESTHESIA WITH HALOTHANE, ENFLURANE, ISOFLURANE OR PROPOFOL

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EFFECT OF SUBLINGUAL BUPRENORPHINE ON GASTRIC EMPTYING OF A LIQUID MEAL

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Buprenorphine is a partial opioid agonist used in the treatment of acute and chronic pain. Adelhoj and colleagues [1] demonstrated delayed gastric emptying after i.v. buprenorphine in volunteers using oral paracetamol methodology. These findings may not be relevant clinically as buprenorphine is often administered sublingually. Furthermore, absorption of paracetamol tablets in subjects with empty stomachs may not reflect accurately gastric emptying of a liquid or solid meal.

Applied potential tomography (APT) can be used to measure the rate of emptying of solid and liquid meals from the stomach [2]. Tomographic images of the resistivity of gastric contents are produced and the rate of emptying is computed. It is necessary to administer a histamine H_2 receptor antagonist before the investigation to inhibit gastric acid production which would affect resistivity measurements. There is a close correlation between APT and scintigraphic measurements [2] after liquid and solid meals. In this study we measured the rate of emptying of a liquid meal ingested after sublingual administration of buprenorphine.

After receiving informed written consent and Ethics Committee approval, six healthy non-smoking volunteers were studied on two occasions separated by at least two days. After an overnight fast, cimetidine 800 mg was given orally and buprenorphine 0.2 mg or placebo was administered sublingually in a double-blind fashion 1.5 h later. Two hours after buprenorphine administration beef consomé soup (Campbells) 250 ml diluted with water 250 ml was ingested at room temperature. Gastric emptying was then measured by APT. Data were collected at 1-min intervals for 40 min. Time to 25% (T_{25}) and 50% (T_{50}) emptying was calculated (table IX). No subject vomited.

TABLE IX. *Individual T_{25} and T_{50} values in the placebo and buprenorphine groups. NR = not reached*

	Placebo		Buprenorphine	
Subject	T_{25} (min)	T_{50} (min)	T_{25} (min)	T_{50} (min)
1	12	26	40	NR
2	9	18	22	39
3	9	16	13	25
4	19	37	NR	NR
5	14	34	13	29
6	NR	NR	NR	NR

These provisional data show that sublingual buprenorphine 0.2 mg delayed emptying of a liquid meal in four of five subjects with normal emptying.

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CAN A COMPUTER HELP WITH PREANAESTHETIC ASSESSMENT?

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The usual preoperative visit the night before surgery may be too late to be effective [1]. Earlier assessment can be costly or use resources inefficiently. One solution may be questionnaires [2] but there may be problems in applying these to elective surgical inpatients. However "computers may be used accepably to gather accurate information" [3] and therefore we developed PASS (Preanaesthetic Screening System) with potential for assessment at the surgical outpatient department.

We developed an interface (computer/patient communication method). Questions and instructions appeared as text on a monitor screen. Patients gave answers via a modified keyboard. Response times and use of an explain facility indicated poor questions. Patients of all ages could use the system. Information obtained was reliable. The method was acceptable to over 80% of patients, although many wanted to qualify or expand on answers.

Appropriate questioning was decided with reference to the literature [1]. A flow diagram of the logic of the system was created with a specified question sequence and actions dependant on answers. Continual patient testing during development led to frequent modification.

In the present system the computer asks a member of staff for identifying details and simple measurements such as height, weight, heart rate and arterial pressure. It then asks the patient directly about areas of direct interest to anaesthetists. A minimum of 55 questions are asked from a total of 126.

Coded answers are stored in memory. At the end of the interview they are analysed and written to disk. A report is printed which summarizes the history and suggests investigations, referrals and simple treatments. Patients can correct errors and the surgeon may use it to help decide preanaesthetic management.

Such early assessment may avoid late operation postponements and expensive "after hours" investigations. The standardized history is useful for research and audit. PASS will never replace preoperative visits but it may reduce uncorrected problems in elective patients.

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COMPARISON OF INTRANASAL SUFENTANIL AND ORAL TRIMEPRAZINE FOR PREMEDICATION OF CHILDREN

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Parenteral premedication causes patient discomfort. Oral premedication is readily accepted by children, but absorption is sometimes unpredictable and presystemic metabolism may occur in the liver. Intranasally administered drugs are not subject to presystemic metabolism. Sufentanil is a potent lipophilic opioid which is absorbed well from the nasal mucosa [1]. We have compared the efficacy of intranasal sufentanil and oral trimeprazine as premedication in children undergoing outpatient anaesthesia.

Fifty-eight day care patients aged 1–10 yr were allocated randomly to two groups: group 1 received trimeprazine 3 mg kg^{-1} orally 60 min and placebo nose drops 30 min before operation; group 2 received placebo syrup orally 60 min before operation and sufentanil 0.5 μg kg^{-1} nose drops 30 min before operation.

The children's behaviour was evaluated on a sedation index (0–4) on admission to the clinic (before premedication), immediately before operation and after operation (the children undergoing tonsillectomy were analysed separately). Responses to venepuncture were evaluated on a scale of 0–3. Arterial pressure, heart rate, ventilatory frequency and arterial oxygen saturation were monitored every 10 min during operation. The duration of apnoea after induction was noted. The same observer, who was unaware of the treatment, made all observations. The data were analysed by Mann–Whitney *U* tests for two samples, chi-square tests for contingency tables and *t* tests for independent samples.

Sufficient sedation was present in both groups (table X). No differences between groups were found for arterial pressure, heart rate, oxygen saturation and ventilatory frequency, except for a slower ventilatory frequency after operation in group 2 (mean 20.71 (SD 3.16) vs mean 25.09 (4.17) $P < 0.05$). Significant differences between groups were found during venepuncture and after tonsillectomy.

Both methods of premedication resulted in adequate sedation. However, intranasal sufentanil provided better postoperative sedation after tonsillectomy, and less reaction to venepuncture. This is probably the result of its strong analgesic properties. Intranasal sufentanil in the dose used did not cause important or life-threatening respiratory depression.

TABLE X. *Sedation score (scale 0–4) after operation and reaction to venepuncture (scale 0–3) in the two groups.* *$P < 0.02$ *compared with group 2 (Mann–Whitney* U *test)*

	Postoperative sedation		Reaction to venepuncture	
Scale	Group 1 ($n = 31$)	Group 2 ($n = 27$)	Group 1 ($n = 28$)	Group 2 ($n = 26$)
0	1	0	7	2
1	4	2	4	1
2	13	5	5	4
3	12	13	12	19*
4	1	7*		

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EFFECT OF LIGNOCAINE ON PAIN DURING INJECTION OF PROPOFOL

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During an initial investigation of propofol we observed that adding lignocaine to the emulsion appeared to be an effective method of reducing pain on injection. Following Ethics Committee approval a double-blind randomized study was performed to test this hypothesis.

One hundred and seventy ASA grade I or II female patients, aged 16–65 yr undergoing minor gynaecological procedures gave written informed consent and were allocated randomly to one of three groups. The patients were not premedicated. Anaesthesia was induced with: propofol 19 ml and 1% lignocaine 1 ml (concentration 0.05%) (group 1); propofol 19 ml and 0.5% lignocaine 1 ml (concentration 0.025%) (group 2); and propofol 19 ml and 0.1% lignocaine 1 ml (concentration 0.005%) (group 3). A control group of unmodified propofol was not included for ethical reasons. All medication was administered via a 23-gauge indwelling needle in a vein on the dorsum of the hand over 40–60 s. After half the estimated induction dose had been injected, the patient was asked if the arm was comfortable and the response was assessed on a four-point scale: 0 = no pain, 1 = sensation only, 2 = discomfort and 3 = pain. One investigator assessed all 170 cases.

After 25 and 50 cases, a preliminary analysis was performed. After 50 cases the incidence of pain in group 3 was 44% (seven of 16 patients) and there was a significant difference between the groups (chi-square = 18.202, $P = 0.0057$). This incidence of pain was regarded as unacceptable and the group was withdrawn. The final results

TABLE XI. *Effect of lignocaine on pain during injection of propofol. Final numbers in groups 1 and 2 include initial study numbers*

	Pain score				
Group	0	1	2	3	Total
First 50 cases					
L1	10	3	5	0	18
L2	9	3	4	0	16
L3	4	1	4	7	16
Total	23	7	13	7	50
Final results					
L1	50	4	22	1	77
L2	45	7	23	2	77
Total	95	11	45	3	154

were analysed without group 3. The overall incidence of pain was 1.95 % (three of 154 patients) and there was no significant difference between the remaining groups (chi-square = 1.44, $P = 0.70$) (table XI).

The study confirms that pain on injection of propofol is reduced by adding lignocaine to the emulsion in a concentration of 0.025 % or greater.

COMPARISON OF RECOVERY CHARACTERISTICS AFTER DESFLURANE AND PROPOFOL FOR DAY CARE ANAESTHESIA

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Desflurane is a methyl ethyl ether, halogenated with fluorine and with a blood-gas partition coefficient less than nitrous oxide (0.42 *vs* 0.46 for nitrous oxide) [1]. This suggests that recovery from anaesthesia should be rapid. We studied the recovery characteristics of desflurane compared with propofol.

Following hospital Ethics Committee approval, a clinical trials exemption certificate and written informed consent, 60 ASA I or II patients undergoing peripheral orthopaedic surgery were entered into the study. All patients were unpremedicated and allocated randomly to one of four groups for induction and maintenance of anaesthesia. In groups 1 and 2 anaesthesia was induced with propofol 2.5 mg kg^{-1} followed by desflurane and nitrous oxide in oxygen for maintenance of anaesthesia (group 1) or propofol infusion 9 mg kg^{-1} h^{-1} for 15 min reducing to 6 mg kg^{-1} h^{-1} (group 2). In groups 3 and 4 anaesthesia was achieved with an inspired concentration of 3–3.6 % desflurane and nitrous oxide in oxygen with 3 % incremental doses of desflurane. All patients were preoxygenated and received tubocurarine 3 mg/70 kg, suxamethonium 1.5 mg kg^{-1}, and fentanyl 1–2 fg kg^{-1}, and the lungs were ventilated to normocapnia. Recovery times (time to open the eyes and respond to commands) were measured. Psychomotor tests (P deletion and digit symbol modalities (DSM)) were completed before anaesthesia and at 30-min intervals for 2 h after operation. Recovery parameters were recorded by a blinded observer.

Patient characteristics were comparable for the four groups. One patient in group 3 and two in group 4 were omitted from analysis as they did not tolerate a gaseous induction. End-tidal concentration of desflurane in groups 1, 3 and 4 at the end of anaesthesia were comparable. The mean times taken for the patients to open the eye's and to respond to the commands, "squeeze my fingers", "tell me your date of birth" and "tell me your name" were longer in group 2 but this was not significant. There was no difference between the groups in the mean times for the patients to sit, stand, walk and tolerate oral fluids The psychomotor scores at 30 min for group 2 were significantly less compared with groups 1, 3 and 4 and at 2 h after operation the scores were significantly different from baseline scores for both the P deletion and DSM tests. No such differences were observed for groups 1, 3 and 4. The incidence of nausea and vomiting in group 2 was less than in the other groups but this was not significant.

This study demonstrates that desflurane provides a fast recovery from anaesthesia and may be a suitable agent for day care anaesthesia.

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IN VITRO COMPARISON OF CSF LEAKAGE AFTER DURAL PUNCTURE WITH HAINDL, SPROTTE AND QUINCKE NEEDLES

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Choice of needle size in spinal anaesthesia is determined by comparing the risk of headache with the technical difficulty of insertion. Post lumbar puncture headache is thought to be related to the rate of leakage of CSF through the hole in the dura mater. Needle size and bevel orientation are generally considered to be related clearly to leakage rate, but studies of bevel design have produced conflicting results. This study was designed to compare the leakage rates of two newly developed bevel designs (Haindl "long" and "short", respectively) with those of some commonly available spinal needles in an *in vitro* model.

Specimens of fresh human posterior lumbar dura (10 cm × 2 cm obtained at autopsy) were secured across six openings in one side of a metal reservoir containing CSF, at a pressure of 15 cm CSF. Six different needles were inserted, each being allocated randomly to one of six positions. Every needle type was inserted (with the bevel orientation parallel to the longitudinal axis of the dura) through 50 different samples of dura. The needle was then removed and the CSF that leaked through each hole was collected over 6 min and weighed.

The results (table XII) confirm that smaller needles allow less leakage of CSF. The 26-gauge long bevel Haindl needle allowed significantly less CSF loss than the 25-gauge Quincke

TABLE XII. *CSF leakage rate for the six needles evaluated.* **P* < *0.05 compared with Haindl short, Quincke 26-gauge, Sprotte and Haindl 24-gauge long*; †*P* < *0.05 compared with Haindl 24-gauge long (Friedman, ANOVA and pairwise comparisons)*

	Quincke 29-gauge	Haindl 26-gauge long	Haindl 26-gauge short	Quincke 26-gauge	Sprotte 24-gauge	Haindl 24-gauge long
CSF loss						
Minimum	0.0	0.0	0.0	0.0	0.0	0.0
Median	0.06*	0.17*	0.33†	0.61	0.65	0.75
Maximum	2.95	2.74	5.99	6.11	5.36	11.05

needle or the 26-gauge short bevel Haindl, but was not significantly different from the 29-gauge Quincke.

The lower frequency of post lumbar puncture headache associated with the use of the 29-gauge Quincke needle is offset by greater technical difficulty. These results suggest that clinical evaluation of the new 26-gauge long bevel Haindl needle is indicated to determine whether the lower rate of CSF leakage seen *in vitro* produces a clinically significant effect on the incidence of post lumbar puncture headache.

COMPARISON OF HIGH AND LOW VOLUME EXTRADURAL INFUSIONS FOR POSTOPERATIVE ANALGESIA

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A variety of extradural infusion techniques for postoperative analgesia have been described [1, 2]. It is well established that the most effective analgesia is achieved using a combination of bupivacaine and an opioid [1, 2] but there is no clear guidance on the best method of administration, different authors using widely different volumes and concentrations of drugs [2, 3]. This double-blind study compared the efficacy and side effects of bupivacaine and diamorphine given extradurally after abdominal surgery. All patients received the same dose of each drug given in one of two volumes.

Forty patients undergoing major gynaecological surgery through a lower abdominal incision took part in the study. Diamorphine 5 mg was given i.m. 1 h before surgery. An extradural catheter was sited at the 10th or 11th thoracic interspace and 2% plain lignocaine 20 ml was injected. General anaesthesia was induced with thiopentone and maintained with 70% nitrous oxide and 1% enflurane in oxygen. Patients breathed spontaneously from a facemask. After 1 h 0.5% bupivacaine plain solution 10 ml was administered through the extradural catheter. Immediately after surgery patients were allocated randomly to receive either a high volume (15 ml h^{-1}) or a low volume (5 ml h^{-1}) extradural infusion. All patients received bupivacaine 18.75 mg h^{-1} and diamorphine 0.5 mg h^{-1}. The patients in the high volume group received a solution of 0.125% bupivacaine and 0.0033% diamorphine. The patients in the low volume group received a solution of 0.375% bupivacaine and 0.01% diamorphine.

Assessments of pain were made at 2, 4, 6, 12 and 21 h after surgery using visual analogue scores. The upper and lower levels of analgesia to pinprick and the degree of motor block in the legs were determined and any side effects were recorded. Patients were withdrawn from the study if they requested further analgesia. Comparisons between groups were made using Mann–Whitney tests with Bonferroni corrections, chi-square or Fisher's exact tests as appropriate.

There were no significant differences between the groups in the number of patients withdrawing from the study, the degree of analgesia, the number of dermatomes blocked, the incidence and degree of motor block in the legs or the occurrence of side effects.

We conclude that the total doses of the drugs used are more important than the volume of solution administered when a combined bupivacaine and diamorphine extradural infusion is used for pain relief after gynaecological surgery.

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COST OF LOW FLOW ANAESTHESIA

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The term low flow is used to refer to a system in which the fresh gas flow is such as to necessitate the use of soda lime. In practice we took this to be a fresh gas flow of 4 litre min^{-1} or less.

The purpose of this study was to discover if a representative anaesthetic department could easily adapt to the routine use of low flow anaesthesia and to measure the economies achieved in practice rather than in theory. The agents studied were enflurane and isoflurane. Northwick Park Hospital spent £37490 on enflurane and £12321 on isoflurane in the financial year 1989–1990.

All members of the department agreed to take part in the study. With the agreement of the anaesthetists concerned, lists were allocated to high or low gas flows. In the high flow group the gas flow rates were sufficient to produce normocapnia using Manley ventilators or exceeded the alveolar ventilation if the Magill system was used.

In the low flow group a conventional circle system (M and IE) was used, with the vaporizer outside the circle (VOC) and the fresh gas flow not exceeding 4 litre min^{-1}.

Inspired oxygen concentration, oxygen saturation and end-expiratory carbon dioxide concentration were monitored routinely. In addition, the peak and trough (end-expiratory) anaesthetic agent concentration was measured continuously using Lamtec 605 agent monitors [1] to which had been attached a display of peak and trough readings derived from the Lamtec [2].

Patients were anaesthetized using standard techniques. Whilst in the anaesthetic room conventional gas flows were used. On entering theatre, patients in the low flow group were connected to a circle system. If controlled ventilation was required, this was achieved using a Penlon ventilator driven by oxygen and attached to the circle in place of the reservoir bag using a length of corrugated tubing whose volume exceeded the tidal volume.

The volumes required to refill the vaporizers throughout the session were recorded together with a detailed record of the gas flow rates and the durations for which these were used. These were between 52 and 93 h of anaesthesia in each group. The reduction in fresh gas flow and rate of anaesthetic agent consumption are shown in table XIII.

Over the study period the cost of enflurane in a low flow theatre was £1.54/h and in a high flow theatre £5.01/h; the respective costs for isoflurane in theatre are £3.40/h and £9.82/h.

At the end of the study a questionnaire was completed by

TABLE XIII. *Median fresh gas flows and rates of consumption of enflurane and isoflurane for high and low flow anaesthetic techniques*

	Enflurane		Isoflurane	
	Low flow	High flow	Low flow	High flow
Median gas flow (interquartile range) (litre min^{-1})	2.9 (1.2)	6.6 (1.0)	2.8 (1.0)	6.4 (1.1)
Rate of consumption (ml h^{-1})	9.5	30.6	8.8	25.5

all members of the department which revealed that 18 of 23 (78%) would be happy to use low flow techniques in routine practice.

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NON-INVASIVE MEASUREMENT OF CHANGES IN CARDIAC INDEX DURING INDUCTION OF ANAESTHESIA

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Cardiac index (CI) and systemic vascular resistance (SVR) were estimated non-invasively using pulsed Doppler ultrasound during induction of anaesthesia with either thiopentone, propofol, methohexitone or etomidate. Ninety-six unpremedicated patients (ASA I) presenting for day care surgery were allocated randomly to receive i.v. alfentanil 0.008 mg kg^{-1} followed 15 s later by a sleep dose of either thiopentone, propofol, etomidate or methohexitone given over 40 s. Loss of eyelash reflex was taken as the end-point for induction of anaesthesia. Arterial pressure was measured using a Dinamap (Critikon) blood pressure monitor. CI was estimated non-invasively with a Velcom 100 (Waters Instruments) cardiac output system. This uses pulsed Doppler ultrasound and a suprasternal transducer. Data are automatically processed giving CI. SVR was calculated from the mean arterial pressure (MAP) and cardiac output.

Baseline values for CI and MAP were averaged from three readings before induction of anaesthesia. Further readings were taken at 1-min intervals for 3 min from the time of induction of anaesthesia. Patients breathed 66% nitrous oxide in oxygen during the study period.

Analysis of variance was used to detect differences between groups. Statistical significance was assumed at the $P = 0.05$ level. Calculations were performed using Macintosh Statworks II software.

Nine patients were excluded from the study for protocol and technical reasons. The mean (SD) dose of induction agent was thiopentone 4.75 (0.85) mg kg^{-1}, methohexitone 1.37 (0.37) mg kg^{-1}, propofol 2.24 (0.41) mg kg^{-1}, and etomidate 0.29 (0.04) mg kg^{-1}. There was no significant difference in baseline MAP, SVR or CI between any of the groups.

Mean MAP decreased significantly from baseline values at 1, 2 and 3 min in all groups. The decrease in mean MAP was significantly greater in the propofol group than in the other groups at 1 and 2 min, and greater than the methohexitone and thiopentone groups at 3 min.

There was a significant increase in mean CI of 8% ($P < 0.01$) in the propofol group and 8% ($P < 0.05$) in the methohexitone group at 1 min which returned to baseline values at 2 and 3 min. There was no significant change in mean CI in the thiopentone group. Mean CI decreased significantly and progressively by a maximum 16% ($P < 0.001$) at 3 min after induction of anaesthesia in the etomidate group

Mean SVR decreased significantly from baseline values at 1, 2 and 3 min in the propofol group by a maximum of 22% at 1 min ($P < 0.0001$). Mean SVR decreased significantly at 1, 2 and 3 min in the methohexitone group by a maximum of 18% at 1 min ($P < 0.001$). There was a decrease in mean SVR (maximum 9% at 1 min) in the thiopentone group but this was not significant. Mean SVR increased significantly at 1 min by 12% ($P < 0.05$) in the etomidate group and decreased towards baseline at 2 and 3 min. The decrease in mean SVR in the propofol group was significantly greater than in the thiopentone ($P < 0.01$) and etomidate ($P < 0.001$) groups at 1 and 2 min and all groups at 3 min ($P < 0.001$ etomidate and $P < 0.05$ thiopentone and methohexitone groups, respectively).

POSTER PRESENTATIONS

NITROUS OXIDE CONCENTRATION IN INTRAVITREAL GAS DURING ANAESTHESIA

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Air and/or inert gases are often injected into the vitreous cavity for internal tamponade as part of vitreo-retinal surgery Anaesthesia with nitrous oxide influences the composition of vitreous gas and intraocular pressure in such patients. Animal studies and computer simulation of intravitreal gas and IOP changes have been reported [1, 2]. This study attempts to quantify the changes in the composition of intravitreal gas induced by nitrous oxide anaesthesia in man.

After Ethics Committee approval, 12 ASA I adult patients (17–71 yr, six males) undergoing routine vitrectomy with fluid–gas exchange were studied. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and muscle relaxation was provided by atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with 65% nitrous oxide, 1% enflurane in oxygen and increments of alfentanil 5–10 µg kg^{-1}. Ventilatory frequency was controlled at 12 b.p.m and tidal volume was adjusted to maintain end-tidal carbon dioxide at 4%. A three-port closed vitrectomy and fluid air exchange was performed. At the completion of the exchange, IOP was measured directly in six patients for 20 min using a calibrated transducer. In all patients 1 ml of intravitreal gas was collected in a glass syringe 20 min after air injection and analysed for nitrous oxide concentration using a mass spectrometer. At the end of the study, nitrous oxide was discontinued and anaesthesia maintained with 2% enflurane in oxygen and increments of alfentanil. Residual muscle relaxation was reversed with neostigmine 50 µg kg^{-1} and glycopyrronium 10 µg kg^{-1}.

Twenty minutes after air injection the range of nitrous oxide concentration measured in intravitreal gas varied from 4–21% (mean 9%). A few minutes after air injection IOP increased to a peak varying from 18–40 mm Hg, but tended to decrease thereafter. This sequence of events was observed repeatedly during the study period with the pressure finally reaching the IOP value noted at the beginning of the study or slightly lower and was associated with gas bubbles escaping from the globe of the eye as observed through the microscope.

Nitrous oxide has a higher blood-gas partition coefficient than nitrogen (0.468 *vs* 0.0147) and its diffusion coefficient in water at 25 °C is also higher (2.6 and 2.01 $cm^2\ s^{-1} \times 10^5$, respectively). Anaesthesia with nitrous oxide leads therefore to a net influx of this gas into the vitreous bubble faster than nitrogen leaves and it may cause a significant increase in intraocular pressure. The reverse can occur after cessation of nitrous oxide at the end of operation and may influence the outcome of surgery. The detection of nitrous oxide in the gas analysed is similar to its diffusion in other gas filled cavities, for example, middle ear and bowels. This influx of nitrous oxide into the gas filled vitreal cavity will lead to dilution and loss of inert gas from the bubble.

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IS SELF-STIMULATION OF P6 FEASIBLE AS AN ANTIEMETIC IN CANCER CHEMOTHERAPY?

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Stimulation of P6 acupuncture point has been shown to be effective in reducing postoperative sickness and as an adjuvant to standard antiemetics in cancer chemotherapy. In both circumstances invasive stimulation–acupuncture (ACP) is slightly more effective than transcutaneous electrical stimulation (TCES). The use of large low impedance (ECG) electrodes has simplified the technique, and alleviated the need for exact placement over the P6 point. This has opened the possibility of self-administration, the feasibility of which has been explored and compared with TCES administered by a doctor.

All patients had experienced troublesome sickness from a previous course of highly emetic chemotherapy despite the use of conventional antiemetics Before the second or subsequent course of therapy, TCES was applied for 5 min (10 or 15 Hz), and repeated at 2-h intervals during waking hours. Patients were instructed to increase the output from the commercial Minitens machine until Qi was experienced. Antiemetics were given as before. Benefit was assessed daily on a four-point scale as described by Dundee and Yang [1].

TABLE XIV *Overall patient benefit in terms of relief of sickness when P6 acupuncture (ACP) or transcutaneous electrical stimulation of P6 point (TCES) by a doctor or patient is combined with standard antiemetics*

	Doctor		Patient
	ACP	TCES	TCES
Benefit	34	27	41
Very good	18	9	13
Good	15	13	23
Slight or nil	1	5	5
Mean (SD)		7.6 (1.6)	11.5 (1.9)

The overall assessment of benefit over 4–5 days in in-patients is shown in table XIV: the findings are compared with published data for ACP [2]. There was no difference in the benefit obtained with doctor and patient administration of TCES ($\chi^2 = 0.65$; $P = 0.72$). ACP gave better results than TCES, but this was not significant ($\chi^2 = 5.71$; $P = 0.0575$ with pooled TCES). There were no complications in either series. Occasional problems arose from drug-induced amnesia and drowsiness, lack of clarity of instructions and complexity of commercially available apparatus.

The use of large electrodes and a simple electrical stimulator could make self-administration of P6 stimulation a clinically useful antiemetic.

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STUDY OF THE EFFECT OF PICOLAX BOWEL PREPARATION ON BODY WEIGHT, CARDIOVASCULAR VARIABLES AND HAEMOGLOBIN CONCENTRATION

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Picolax is a combination of magnesium citrate 16.2 g, an osmotic laxative and sodium picosulphate 10 mg which when hydrolyzed in the colon acts by decreasing water and electrolyte absorption in the large bowel and increasing intestinal motility [1].

Ten patients were given two sachets of Picolax 6–12 h apart before surgery and were matched with 10 controls for age, weight and ASA status. Body weight, supine arterial pressure

TABLE XV. *Mean (SD) changes in body weight and cardiovascular parameters in the Picolax and control groups. Significant differences within group:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; *compared with control:* †$P < 0.05$, †††$P < 0.001$

	Picolax group	Control group
Age (yr)	65.3 (range 42–78)	64.2 (range 40–78)
Weight loss (kg)	2.28 (0.58)***†††	0.39 (0.38)**
Change in haemoglobin	+0.65 (0.59)*†	+0.15 (0.33)
Change in packed cell volume	+0.018 (0.028)	+0.004 (0.007)
Arterial pressure (mm Hg)		
Systolic standing before	151.6 (21.1)	154.4 (32.9)
% decrease after Picolax	12.9 (13.8)*	5.8 (5.2)**
Heart rate (beat min^{-1})		
Standing before	77.0 (14.9)	70.6 (11.5)
Standing after	92.2 (19.5)**†††	70.4 (11.5)
Supine before	70.2 (16.0)	66.8 (11.6)
Supine after	78.6 (12.7)*†	63.5 (13.7)

and heart rate (mean of three measurements taken at 3-min intervals), standing arterial pressure and heart rate (mean of three measurements taken at 1-min intervals), haemoglobin concentration and packed cell volume were made before administration of Picolax or on the evening before surgery for the control group. Both groups received oral fluids *ad libitum* until midnight before surgery and were then starved until the time of surgery. All measurements were repeated before premedication. Analysis was by Students *t* paired and unpaired *t* tests as appropriate.

There were no significant differences in diastolic or supine systolic arterial pressure before or after treatment in either group. Picolax induced a reduction in weight and body fluid of approximately 2 kg. The cardiovascular changes suggest that intravascular volume was decreased but the patients studied were able to partially compensate by increasing heart rate on standing (table XV).

Care should be exercised in the administration of Picolax to patients with cardiovascular impairment and consideration should be given to parenteral fluid replacement. The quantity and type of replacement fluid remains to be determined.

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CONTINUOUS SPINAL ANAESTHESIA WITH A 28-GAUGE CATHETER

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Continuous spinal anaesthesia with a catheter technique promises the advantages of regional block for extended operative periods. We report on a preliminary assessment of the ease of initiation, efficacy and acceptability of the technique in 26 surgical patients.

Following Ethics Committee approval 26 patients (17 male, aged 40–80 yr) undergoing elective major orthopaedic, abdominal and vascular surgery were entered into the study. The 28-gauge Kendall CoSpan catheter was placed through a 22-gauge spinal needle in the L3–4 interspace. Two to three centimetres of catheter was inserted into the subarachnoid space and 0.5% hyperbaric bupivacaine 0.5 ml was administered through the catheter with the subject in the supine position. After 10 min further increments of 0.1–1.0 ml were given to achieve the desired level of block. Sensory loss, motor block and cardiovascular parameters were assessed at 5-min intervals. During the operation the block was maintained by 0.25-ml increments every 45 min.

A successful block was established in all 26 patients. The procedure was unsuccessful in two patients in whom it was impossible to thread the catheter, despite a definite CSF tap. In these two patients a single dose of local anaesthetic was administered through the spinal needle and the operation proceeded uneventfully. General anaesthesia was supplemented in 16 patients and the rest received light sedation. The mean initial dose necessary to establish the block was 0.5% hyperbaric bupivacaine 0.8 ml (SD 0.4 ml). The maximum height of block was T4, the median height of block was T10 and the lowest height of block was T12. The total dose administered ranged from 0.5 to 2.5 ml. Time of onset to block was rapid in most cases: 3 min in three patients, less than 7 min in 12 patients, up to 10 min in nine patients and greater than 10 min in only two patients.

Hypotension (< 90 mm Hg systolic or a 30% decrease) occurred in three subjects and was treated with ephedrine. Twenty-four-hour follow-up yielded no neurological sequelae. Maximum maintenance of block was 4.5 h. In one subject the catheter broke on removal. Approximately 2 cm of the tip was left subcutaneously and no complications developed.

This technique seems well suited to an easily and rapidly initiated regional block. The technique is flexible in that satisfactory anaesthesia was maintained for up to 4 h. Low doses of local anaesthetic were required; the initial block was established with bupivacaine 0.5 ml in nearly 50% of the group. Resistance to threading the catheter through the needle is a recognized reason for failure, and gives rise to initial technical difficulties. However, familiarity with the procedure leads to an improved success rate. The two failures occurred within the first 10 patients, and none subsequently. Other groups have reported that with appropriate attention to technique, postdural puncture headache [1] and infection [2] are unlikely.

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EFFECT OF PROPOFOL AND ETOMIDATE ON THE CONVULSIVE ACTION OF LAUDANOSINE IN MICE

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Laudanosine, a major metabolite of atracurium has been shown to cause CNS excitation and convulsions in laboratory animals [1]. Previous studies have demonstrated that propofol [2] and etomidate [3] have anticonvulsant properties similar to thiopentone using pentylenetetrazole and the electroshock test. The purpose of this study was to determine the effect of propofol and etomidate on convulsions induced by laudanosine.

Experiments were conducted on female MF1 mice. All injections (i.v.) were carried out using 27-gauge butterfly needles (Abbott) and a specially designed mouse restraining device. Propofol was prepared by diluting the aqueous emulsion formulation (Diprivan) with normal saline before i.v. injection Control mice were given equal volumes of normal saline or diluted 10% Intralipid (KabiVitrum) with normal saline. Etomidate (Hypnomidate) was administered diluted with saline and control mice received equal volumes of 35% propylene glycol or saline. Laudanosine (Sigma) was injected as 2 mg ml^{-1} solution through another tail vein. All animals were killed immediately after seizure had been induced and the dose of laudanosine required to induce convulsions was calculated for each animal. The group mean minimum convulsant dose (MCD) and SEM of not less than eight mice was calculated for each group and statistical analysis was performed using the Mann–Whitney *U* test in concurrently tested mice. $P < 0.05$ was considered significant.

Propofol 10, 20 and 30 mg kg^{-1} caused a significant dose-related increase in the MCD of laudanosine compared with normal saline or Intralipid. Etomidate 6.7 mg kg^{-1} caused a significant decrease in the MCD of laudanosine compared with normal saline or propylene glycol whilst lower doses had a small but significant anticonvulsant effect (table XVI).

These results indicate that propofol (in subhypnotic and hypnotic doses) has a protective effect against convulsions induced by laudanosine while etomidate enhanced or reduced the convulsive action of laudanosine dependent upon the dose used.

TABLE XVI. *Minimum convulsant dose (MCD) of i.v. laudanosine 2 min after propofol or etomidate. Control results have been bulked for brevity. (Mean (SEM)).* *$P < 0.05$ *compared with concurrent vehicle control*

Group	MCD (mg kg^{-1})	No. of mice
Normal saline	16.86 (0.44)	30
Intralipid	17.91 (0.45)	24
Propofol 10 mg kg^{-1}	23.42 (1.00)*	8
Propofol 20 mg kg^{-1}	26.85 (1.45)*	8
Propofol 30 mg kg^{-1}	28.68 (0.60)*	8
Propylene glycol	17.59 (0.50)	42
Etomidate 2.5 mg kg^{-1}	21.78 (0.47)*	10
Etomidate 5 mg kg^{-1}	18.78 (1.03)	10
Etomidate 6.7 mg kg^{-1}	13.72 (0.40)*	22

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SILENT MYOCARDIAL ISCHAEMIA AND MYOCARDIAL DYSFUNCTION IN PATIENTS UNDERGOING AORTIC RECONSTRUCTIVE SURGERY

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Ambulatory ST segment monitoring is a reliable method of detecting myocardial ischaemia [1]. There is evidence to suggest that silent ischaemia provides independent prediction of adverse outcome in stable and unstable angina, as well as in the postoperative period in non-cardiac vascular surgery [2]. The aim of our study was to determine whether silent myocardial ischaemia is related to myocardial function in patients undergoing elective aortic surgery.

Twenty-four consecutive elective admissions for aortic reconstructive surgery were studied after informed consent had been obtained. Patients were fitted with a solid state ambulatory ECG recording device. Data were interpreted using a purpose-designed program on an IBM AT computer and edited by a human observer. Greater than 60 s of ST depression of over 1 mm was considered significant with each episode terminated by a 1-mm return to baseline Patients were further studied with a radionuclear gated heart pool scan to ascertain indices of myocardial performance and evidence of myocardial damage. Patients with left bundle branch block, left ventricular hypertrophy, and those receiving digoxin therapy were excluded.

The gated heart pool scans revealed myocardial abnormalities in 62.5% of the selected patients, which consisted of evidence of either past myocardial infarction or wall motion abnormalities suggestive of ischaemia. In addition, some 20.8% of the population had ventricular ejection fractions of less than 40%; none of these patients was from the group without radionuclear evidence of ventricular damage. Similarly, the incidence of silent myocardial ischaemia was 29.2%, clustered strongly within the population with evidence of ventricular damage. Comparison of the patients with ejection fraction greater ($n = 19$) or smaller ($n = 5$) than 40% and the presence or absence of silent ischaemia shows a significant association of low ejection fraction and silent ischaemia ($P < 0.05$) (table XVII).

Our study has demonstrated a high incidence of myocardial damage and dysfunction in patients presenting for aortic surgery and shown an association between silent ischaemia and

TABLE XVII. *Relationship between silent ischaemia and ventricular ejection fraction*

	Ejection fraction		
	< 40 %	> 40 %	Total
Silent ischaemia			
Present	4	3	7
Absent	1	16	17
Total	5	19	24

poor ventricular function. A preoperative ambulatory ECG free of ischaemia is, moreover, associated with less likelihood of pre-existing ventricular dysfunction and a low risk of postoperative cardiac morbidity [2]. We conclude that ambulatory ECG monitoring may be an effective non-invasive method of detecting high risk patients from an asymptomatic group presenting for major vascular surgery.

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HALOTHANE AND ISOFLURANE ANAESTHESIA REDUCE CARDIAC INDEX IN THE ELDERLY

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Elderly patients are known to be more sensitive to the cardiovascular effects of volatile anaesthetic agents than young adults. Isoflurane may be preferred to halothane for these patients because of its lower biodegradation, lower blood solubility, and cardiovascular stability [1] in the young. However, the effect of isoflurane on cardiac output has not been documented in elderly patients.

Forty ASA I or II patients, aged 60 yr or more and within 20 % of their predicted lean body mass, were studied following Ethics Committee approval and informed consent. Patients were excluded if they were receiving any cardioactive medication, had a past history of ischaemic heart or respiratory disease or recent halothane exposure. One hour after benzodiazepine premedication, baseline measurements of systolic, diastolic and mean arterial pressures (SAP, DAP, MAP), and heart rate (HR) were made using a Datascope Accutorr

Measurements of cardiac output (CO) were made using a Datascope Accucom and cardiac index (CI) derived from this. Anaesthesia was standardized and consisted of etomidate 0.3 mg kg^{-1} for induction followed by atracurium 0.5 mg kg^{-1} to facilitate tracheal intubation. Initial maintenance was with increments of etomidate. Two minutes after intubation (time 0), halothane ($n = 20$) or isoflurane ($n = 20$) was introduced by random allocation. The lungs were ventilated to normocapnia with oxygen. Measurements of SAP, DAP, MAP, HR and CO were made at time 0 and every 2 min for 20 min. During this time, volatile agent concentration was adjusted to rapidly achieve and maintain 1 MAC expired concentration (0.65 % halothane, 1.05 % isoflurane). Statistical analysis was by unpaired Student's t test and repeated measures analysis of variance with $P < 0.05$ considered significant.

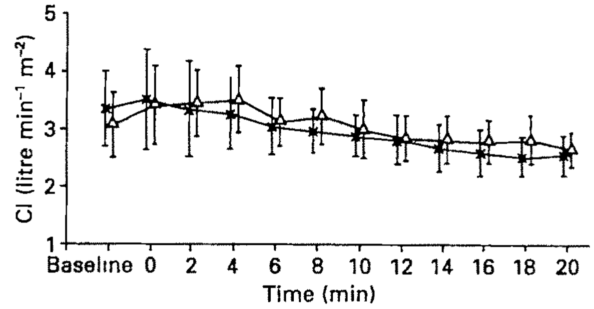

FIG. 4. Mean cardiac index (CI) and 95 % confidence limits following isoflurane (×) and halothane (△) anaesthesia in elderly patients.

There were no significant differences between the groups in respect of patient characteristics or baseline measurements (mean age 70.9 yr, SD 6.47). There was a significant reduction with time of all values, including CI, in both groups (fig. 4). Isoflurane caused a greater decrease in SAP, MAP and DAP compared with halothane, but only the difference in DAP was significant.

Both isoflurane and halothane appear to reduce cardiac index, but isoflurane produced a greater decrease in diastolic pressure than halothane in the elderly population

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VARIATION OF PLASMA GLUTATHIONE S TRANSFERASE CONCENTRATION IN HEALTHY VOLUNTEERS

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Previous studies [1, 2] have shown that plasma concentrations of hepatic glutathione S transferase (GST) increase after anaesthesia with halothane or enflurane. We have suggested that this indicates subclinical liver damage but have to exclude the possibility that such increases might be associated with fasting or diurnal variation.

Thirty healthy volunteers (nine female) aged 24–49 yr (mean 32 yr) fasted overnight. A blood sample for GST, alanine aminotransferase (ALT), and γ glutamyl transferase (γGT) was taken at approximately 09.00 the next day (time 0). Further samples were taken 3, 6, and 24 h after this initial sample, time intervals that corresponded to those of previous studies of patients undergoing anaesthesia.

TABLE XVIII. *Median and interquartile ranges of gluthathione S transferase concentrations* (μg *litre*$^{-1}$) *at study times.* *P < 0.05 *compared with time 0*

	Time (h)			
	0	3	6	24
Median	1.9	1.7*	1.9	1.9
Interquartile range	1.4–2 6	1.3–2.1	1.4–2.1	1.5–2.6

Two volunteers had GST concentrations that were not within the reference range. The results for these subjects were considered separately.

The median and interquartile ranges of GST concentrations at each sampling time are shown in table XVIII. The Wilcoxon signed rank test was used to examine differences relative to the value at time 0. The median GST value at 3 h was significantly reduced ($P < 0.05$). This contrasts with the changes found in patients after anaesthesia. Two volunteers had a GST value greater than the upper limit of the reference range. This occurred at 3 h in one patient and at 24 h in the other. The two volunteers who had abnormal initial values showed a similar pattern of changes.

We have confirmed that there is no marked increase in GST in association with fasting and possible diurnal variation. Increases in GST following anaesthesia therefore probably indicate transient hepatic damage.

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British Journal of Anaesthesia 1991; **66**: 415–417

CORRESPONDENCE

TRANSDERMAL HYOSCINE AND POSTOPERATIVE NAUSEA AND VOMITING

Sir,—I refer to the recent double-blind comparison by Koski and colleagues [1] involving different types of surgery, in which transdermal hyoscine was found to be of no benefit in reducing the incidence of nausea and vomiting after operation. A recent study by Bailey and colleagues [2] concluded that transdermal hyoscine was an effective antiemetic in patients undergoing outpatient laparoscopy. This appears to be in accordance with the account given by Palazzo and Strunin [3] which described a lower incidence of nausea and vomiting in gynaecological operations than in intra-abdominal operations.

The strength of opioid analgesia used may be significant. The doses of fentanyl used by Koski [4] (3–5 $\mu g\ kg^{-1}$) were greater than those used by Bailey and colleagues [2] (0.5–2 $\mu g\ kg^{-1}$), and a previous study in which less potent analgesia was used (morphine and pethidine) [5] found transdermal hyoscine was effective even in patients undergoing different types of surgery. These limited studies on the prophylactic use of transdermal hyoscine suggest that its effectiveness may be affected by the potency of analgesia used.

B. J. Hendley
London

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Sir,—Thank you for the opportunity to comment on Dr Hendley's letter.

The strength of opioid analgesia may certainly affect the incidence of postoperative nausea and vomiting. A tendency towards such a finding was noted also in our original study [1]. However, more extensive surgery was performed on the majority of patients in our study. Thus the group of patients receiving low doses of opioids was too small for statistical evaluation.

In a study just completed, we induced and maintained anaesthesia in a way similar to that described by Bailey and colleagues [2], but administered only 0.1 mg of fentanyl to inpatients undergoing laparoscopy. In recovery, only 5% of these patients vomited and no more made spontaneous complaints of nausea. Only when questioned specifically, 15% admitted feeling nauseated. In the postoperative ward, 15% of patients vomited within the first 8 h after operation. However, solid food was tolerated by 65% and liquids by 30% at the evening meal time. These initial results suggest that the tendency to nausea, vomiting, or both, may be reduced by maintaining anaesthesia mainly with inhalation anaesthetic agents and limiting the peroperative dose of analgesics.

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FAILED TRACHEAL INTUBATION

Sir,—I should like to add one or two comments to the excellent review by King and Adams [1]. White and Panjabi [2] believe that flexion/extension movements at the atlanto-occipital and atlanto-axial joints are more or less equal and that they function as a unit, "the occipito-atlanto-axial (OAA) complex". King and Adams appear to suggest that bone structure limits movement at the OAA complex. I expect they refer to diseased patients (congenital or acquired), as flexion/extension movements of the OAA complex are not limited normally by abutment of the bones but by the tectorial membrane, which is the prolongation of the posterior longitudinal ligament inserted on the anterior rim of the foramen magnum. This accounts for those patients, with clinically poor top end movement, who have radiographically satisfactory separation of C0, C1 and C2.

We are performing a prospective study of difficult intubation in patients with diseased cervical spines. It is already quite clear that an absent atlanto-axial gap is a more powerful discriminant than an absent atlanto-occipital gap. Flexion/extension lateral radiographs are required to diagnose an absent gap [3]. A "neutral" view is acceptable if there are good gaps, but when they appear to be absent, one questions if it was a truly neutral position.

I. Calder
London

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STUDIES ON MIVACURIUM

Sir,—Data published in the *Canadian Journal of Anaesthesia* [1] were used as a comparison group in two subsequent papers [2, 3]. One paper [2] made a comparison with a new group of patient data, whereas the other [3] reported use of a unique statistical treatment to analyse data among groups.

In the first paper [1], a more thorough treatment of the effects on both neuromuscular block and circulation caused by mivacurium during nitrous oxide–opioid anaesthesia was compared with those in patients receiving mivacurium during nitrous oxide–isoflurane anaesthesia. (Ninety patients were described in the nitrous oxide–opioid group; the first 45 patients from the nitrous oxide–opioid group were used as a comparison group in the other two papers. The last 45 patients in the paper in the *Canadian Journal of Anaesthesia* [1] were given doses which exceeded the ED_{95}.) We used data from those patients who received mivacurium 0.03–0.15 mg kg^{-1} during nitrous oxide–opioid anaesthesia so as to provide comparison data for our studies during other types of anaesthesia. We failed to clarify this by appropriate references in subsequent papers.

In the third paper [3], slopes and intercepts of the dose–response curves for mivacurium during the three types of anaesthesia were compared using a *t* test for multiple comparisons described by Winer and noted as reference No. 8 in this paper. This analysis is not found in either of the other two papers.

We were in error in failing to acknowledge that data from 45 patients were common to all three papers and that data from an additional 45 patients (anaesthetized with isoflurane) were common to two papers [1, 3]. We should have asked permission from the *British Journal of Anaesthesia* to use these data for comparisons in our other manuscripts. Copies of the other manuscripts should have been included for each Journal's review at the time of original submission and they should subsequently have been cross-referenced correctly. We apologize for this error.

Finally, we have thought carefully about the sequence of events which occurred here and have tried hard to understand our actions and our *intent*. We had no *intent* to deceive. This was a large project, with 171 patients studied. The three manuscripts were all prepared and submitted at about the same time (February 21 to March 7, 1989) and we failed to ask for permissions or cross-reference them correctly. The data are true and correct responses to mivacurium during three types of anaesthesia.

R. P. From
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W. W. Choi
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PROPOFOL: EFFECT ON THE MYOCARDIUM COMPARED WITH THE PERIPHERAL VASCULAR SYSTEM

Sir,—I read with great interest the article by Boer and colleagues [1] on the effect of propofol on peripheral vascular resistance during cardiopulmonary bypass. The authors state that propofol appeared to cause more hypotension than an equivalent dose of thiopentone, and that this may be related to the greater decrease in peripheral vascular resistance (PVR), citing my study [2] in their opening paragraph. They continue to say that the decrease in PVR was comparable to the decrease in arterial pressure, suggesting that vasodilatation may be a major factor in propofol-induced hypotension.

I believe the authors are incorrect in what they state. The study plainly revealed no significant decreases in either PVR or SVR, but significant decreases in left cardiac work index and left stroke work index of 35%. Cardiac index decreased by 18%, while mean arterial pressure decreased 23%. The data indicate myocardial depression without loss of systemic vascular resistance. Authors such as Williams and colleagues [3], Kaplan and colleagues [4] and Van Aken and colleagues [5] have also indicated that propofol is indeed a myocardial depressant drug.

Dr Boer and his colleagues are to be congratulated on performing such an interesting study and also on their statement that the results are influenced by special factors present during cardiopulmonary bypass, in particular haemodilution, hypothermia and the use of non-pulsatile blood flow. Data resulting from the use of drugs during cardiopulmonary bypass to determine their effects on the vascular bed are, indeed, difficult to extrapolate to the intact human being.

M. Lippmann
Los Angeles

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Sir,—Thank you for the opportunity to reply to the letter from Dr Lippmann.

In many, but not all studies investigating the cardiovascular effects of propofol, the reduction in arterial pressure was accompanied by a decrease in peripheral vascular resistance. In the study by Dr Lippmann and his colleagues [1], vascular resistance decreased from mean 2007 (SEM 111) dyn s cm^{-5} before propofol to 1781 (127) dyn s cm^{-5} 2–3 min after induction. As Dr Lippmann rightly points out, this decrease was not statistically significant, and we apologize to him and his colleagues for misquoting them.

There is indirect [1, 2] and direct [3, 4] evidence that propofol results in myocardial depression, but the extent to which this contributes to propofol-induced hypotension remains unresolved. It is also uncertain whether the decrease in contractility is caused by a direct effect of the drug on cardiac muscle, is secondary to a decrease in coronary perfusion resulting from hypotension [2] or is the result of a mismatch in oxygen supply and oxygen demand [3]. There is clearly a need for more fundamental research into the influence of propofol on cardiac muscle.

F. BOER
P. ROS
J. G. BOVILL
P. VAN BRUMMELEN
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Leiden

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RAMON Y CAJAL

Sir,—While I much enjoyed your first Editorial in the November issue [1], I think you will find that the 1894 Croonian Lecture was given by the distinguished Spanish histologist Ramon y Cajal.

B. E. WALSH
Newcastle

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The error in this article occurred at the sub-editing stage. We apologize to the authors and we are pleased to find that the *Journal* is scrutinized so carefully!

Editors

British Journal of Anaesthesia 1991; **66**: 418–419

BOOK REVIEWS

Clinical Oxygen Pressure Measurement II. Edited by A. M. Ehrly, W. Fleckenstein, J. Hauss and R. Huch. Published (1990) by Blackwell Ueberrenter Wissenschaft, Berlin. Pp. 436; illustrated. Price £110.00.

This volume contains the proceedings of two meetings on Oxygen Measurement, held in Germany in 1988. Most of the topicality has been lost in the more than 2-year delay to publication. The 58 contributions cover a wide range of topics of clinical and experimental interest and comprise summaries of original work and brief reviews. The bulk of the work has made use of the Po_2 electrode for measurement of oxygen tension in tissues as diverse as brain, myocardium, lung surface, kidney and skeletal muscle. The theoretical basis and practical difficulties of the measurements are highlighted by the work of Schramm and colleagues on the physical effects of the electrodes on skeletal muscle. Electron micrographs elegantly display the damage caused to the tissue and thus bring into question the interpretation of the Po_2 values obtained.

The cover of the book suggests that it will be of value to the anaesthetist or intensive care physician by presenting an "update" of the field. Several factors militate against this aim. The delay between presentation and publication is such that much of the work will probably have been published elsewhere in a more complete form. Despite the use of English language advisers, the text still contains a number of uninterpretable words and phrases. The most serious defect is the lack of an index, and the reader searching for information in his particular field will experience difficulty in locating relevant material.

Those with an interest in this field will find much useful work, but which may already have reached their attention. The lack of an index ensures that the volume can not be recommended for general library purchase.

C. D. Hanning

Malignant Hyperthermia Neuromuscular Diseases and Anaesthesia, 1st Edn. Edited by W. Mortier and E. Breucking. Published by Georg Thieme Verlag, Stuttgart. Pp. 100; indexed; illustrated. Price DM 40.00.

This small book contains the proceedings of an international symposium on anaesthetic problems in patients with malignant hyperthermia (MH) and other neuromuscular disorders, held in Wuppertal, West Germany in May 1989. There are 13 short chapters, all by European authors, with the majority from West Germany. The topics discussed vary from the dated, the importance of serum creatine kinase values, to the most modern, the molecular genetics of MH. In general there is little in most chapters that is not covered more than adequately in standard anaesthetic textbooks or in recent review articles.

The two most notable chapters are on the molecular genetics of MH and the social, legal and genetic aspects of the syndrome. The novelty of the former has been negated by the full publication of the data earlier this year in *Nature* (*Nature* 1990; 343: 559–561, 562–564). Nevertheless, there is some interesting information about previous work suggesting linkage of halothane susceptibility with other genes. I was left with the impression that the Scandinavian agricultural geneticists in the mid-1970s accurately ascertained the linkage with other genes in the porcine model and that the intervening period has been spent in waiting for the production of suitable polymorphic DNA markers to determine the site of the human MH gene on chromosome 19.

In complete contrast, Ellis describes the social, legal and genetic implications of MH in a chapter full of good sense based on extensive knowledge, both practical and theoretical. He steers a steady course through the eccentric fringes of MH, of which there are many, pointing out the irrationality of several opinions that have been published on the subject.

I cannot recommend this book. There is nothing in it for the research worker or for the clinician.

G. M. Hall

Outpatient Anaesthesia. Edited by P. F. White. Published by Churchill Livingstone, New York. Pp. 520; illustrated. Price £47.50.

This is a multi-author textbook edited by Professor Paul F. White from the Washington University School of Medicine, St Louis, Missouri. He is an acknowledged authority on outpatient (ambulatory) surgery. A total of nine professors have contributed chapters in the book. Duplication is inevitable in such a text, but does not diminish the value of this impressive book. It will have great appeal to anaesthetists, surgeons, nurses and hospital managers, for it presents a concise account of day surgical practice.

The British reader will be impressed by the explosion of day surgery in America over the past 20 years. There are now 1000 hospital-affiliated ambulatory centres in the U.S.A. and 40% of all operations are performed in these facilities. This contrasts with the British scene, where day surgery continues to expand at a slow pace. Perhaps the establishment of at least one teaching day centre in Britain could suitably hasten further expansion?

The book is hard-backed and at £47.50 is good value. The diagrams and tables are well produced and the references are a mine of information. Readers are given examples of day unit design, anaesthetic record sheets and patient information literature. Undoubtedly, these will assist any doctor given the responsibility of planning and directing a day facility.

Professor White has written the first chapter and it is an excellent overview of current Outpatient Anaesthesia. This chapter is fully referenced and covers the salient features of general and local anaesthetic techniques for day surgery. More importantly, White poses several questions for future research, for example does the duration of surgery adversely affect postoperative morbidity and how long should preoperative starvation last?

There are good chapters on the organization, economic and medico–legal implications of outpatient anaesthesia. However, the chapter on nursing methods deserves mention. It is written by nursing personnel from St Louis, Missouri and Melbourne and it clearly emphasizes the important role played by nurses in the day-to-day management of ambulatory centres. The section on education is particularly relevant if day surgery is to expand in Britain.

There are two topical chapters on paediatric and geriatric day surgery. Apparently age is no barrier and geriatric patients should be judged on physiological rather than chronological age. Certainly, with the increasing number of elderly in Britain, the chapter on geriatric day case anaesthesia is both appropriate and worthy of further study.

As rapid, reliable patient recovery following day surgery is important, a chapter by Dr Kari Kortilla, an authority on recovery, is most welcome. All aspects of recovery testing are evaluated, but no single test is recommended for all patients. Dr Kortilla clearly states that patients should be discharged from day units only if they comply with common sense clinical criteria such as stable vital signs, the ability to walk, etc.

Perhaps the most relevant chapters in this book are written by White on postoperative analgesia and Epstein on controversies in outpatient anaesthesia. White outlines the significant advances in the analgesic field and calls for more research into appropriate analgesic delivery systems for the home environment. Epstein touches on every day problems in the ambulatory field, for example methods of preoperative patient selection, risk factors involved and investigations required before surgery. Aspects of anaesthetic practice such as the necessity for premedication, prophylaxis against vomiting and aspiration, and patient monitoring are all debated. Epstein also gives his considered opinion on whether patients for laparoscopy should undergo intubation and ventilation, and attempts to identify when conscious sedation becomes general anaesthesia.

The immense value of this textbook is that it presents the current state of the art of Outpatient Anaesthesia. Such a book will be of value to all British doctors and nurses involved in the field of day surgery. It is a readable, well-researched book and clearly presents the challenges facing day unit personnel. It should be available in all British day surgery units, anaesthetic departments and medical school libraries.

T. W. Ogg

Mastering Infrared Capnography, 1st Edn. By Z. Kalenda. Published (1989) by Kerckebosch BV, Zeist, The Netherlands. Pp. 267; indexed; illustrated. Price Nl.Fl.215.

This extraordinary book is concerned with carbon dioxide and its measurement by infra-red capnography in anaesthesia and intensive care. The physiology of production, transport and excretion of carbon dioxide is described, together with the principles and clinical applications of infra-red carbon dioxide analysers. I describe the book as extraordinary because each page consists of a figure, with a few lines of explanation underneath. It gives the impression that slides from a series of lectures have been transposed into print and the explanation of each slide appended underneath. This results in a book which is easy to read in a very short time.

Many points are explained beautifully because of the high quality of the illustrations, but many figures are unnecessary and add bulk to the book. I estimate that if the latter figures were removed, the book would be reduced in size by about 50%. There is no in-depth discussion of many of the subjects covered in this book, but the basic principles are explained extremely well.

The best feature of this publication is the collection of capnographs demonstrating many clinical applications. The author has obviously spent many years collecting these tracings. Other areas of clinical interest where capnography is illustrated include high frequency ventilation, heart–lung bypass, the use of double-lumen endobronchial tubes and typical tracings after equipment malfunction.

It is difficult to recommend this book unreservedly, as many would consider the format of the book a little strange and the content rather didactic and over simplistic. Personally, I have found it a delight to read and my belief that capnography is of considerably more use than simple monitoring of ventilation during anaesthesia has been reinforced.

D. J. Rowbotham

An Introduction to Cardiovascular Physiology. By J. R. Levick. Published (1991) by Butterworths. Pp. 279; indexed; illustrated. Price £14.95.

The *understanding* of cardiovascular physiology is the theme of this excellent book by Dr Levick, Reader in Physiology at St George's Hospital Medical School, London. He starts from the "why" and proceeds to the "how", using a wealth of experimental and clinical examples in 15 chapters covering all aspects including electrophysiology and interstitial fluid interchanges. The volume is intended for students of medicine and physiology, but the depth of material is sufficient as a basic text for trainee anaesthetists. Those contemplating the Parts 1 and 2 of the F.C.Anaes. would do well to read this volume first. They would obtain a more than basic understanding of cardiovascular physiology and then could add the details of the changes with anaesthesia and disease from relevant texts.

The book is produced to a high standard and is well illustrated and indexed. The price is modest and it deserves a place, not just on the shelves of department libraries, but also in the personal collections of both trainees and their teachers.

C. D. Hanning

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